"The Surgical Aspects of Water and Salt Metabolism."

by

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CHAPTER I.

THEORETICAL CONSIDERATIONS.

It has been realised since the dawn of history and the birth of medicine that water plays a part of unequalled importance in the economy of living organisms. Its overweening necessity has forced man and all living thi ngs, either to seek it urgently or to create in themselves and their descendants means whereby it may be conserved. The water storing function of the camel's hump enables the ship of the desert to live for days without water in an arid waste; the cactus plant serenely lives and grows and multiplies in conditions which would blast the lily in a few hours; clothes moths and snakes can exist for long periods on the water liberated by the metabolism either of ingested food or of their own body substance; and, an even more remarkable adaptation of life to living under dessicating conditions is that of the hygroscopic spines of certain lizards, notably the Moloch lizard of Australia, the horned toad (phrynosoma) of California, and the starred lizard (Agama Stellis) of Asia Minor. Indeed, it has been aptly said that in the countless years since life first was born in the oceans of the world, the history of its gradual and progressive elaboration of form and function is the story of life's many adaptations to the special purpose of conserving water, thus making itself more independent of changing environmental conditions. Therefore, knowledge of the metabolism of water is essential to our understanding of the processes of life.

The importance of the subject was first realised by the"humourists" of Greek medicine; it was the first physiological problem to be investigated quantitatively, by the use of the balance in the hands of the Alexandrians Menon and Erasistratus, and later, in 1614, by Sanctorius (1). In more modern times, and especially in the last two decades, many investigators have sought the secrets of water metabolism. But, in spite of these many years of investigation, it is only recently that some of the details of water absorbtion, partition, utilisation and excretion have been revealed; and, under abnormal conditions od disease and deranged function, the part played by water imbalance, both in the pathology of the disease itself and in the production of clinical symptoms and signs is only today beginning to be understood. The physiology of water is thus a problem at once ancient and recent.

The metabolism of water is inseparably interwoven with the metabolism of the many substances which exist either in solution or suspended in the water of the body. This complex system of water, dissolved and suspended substances, is known as the body fluid. For descriptive purposes and also because of definite differences of composition and function, the body fluid has been divided into two main fractions:

A. The Intracellular Fluid which exists inside the body cells.

B. The Extracellular Fluid which exists outside the body cells in the various extracellular spaces i.e., blood vessels, lymph vessels, the spaces between the body cells collectively called the interstitial space, in the various serous compartments of the body- peritoneal,pleural, subarachnoid, and joint spaces, etc.

It will be seen that these two main fractions of the body fluid are separated by the semipermiable cell membrane. Although intracellular fluid differs from extracellular fluid in composition, and the intracellular fluids found in muscle cells, liver cells, the cells of the nervous system,etc., all vary in composition, there exists a state of osmotic equilibrium between the intracellular and extracellular fluids all over the body.

The several extracellular fluids also in greater or less degree are separated by cell barriers and themselves differ in composition. Thus blood plasma, lymph, cerebro-spinal fluid, synovial fluid,etc. all have different compositions the details of which will be discussed later.

For clarity of description, it is necessary partially to separate the various constituents of the body fluids into two main fractions- the water itself and the various substances either dissolved ro suspended in this water. But it must be emphasised that neither the water nor its solutes can be individually affected by changing conditions of ingestion or excretion. Alteration in the body content of the one inevitably causes changes in the amount and concentration of the other. Always remembering this important conception, the metabolism of water,mainly in its surgical aspects, will be discussed first. The metabolism of certain of the dissolved substances, notably sodium chloride, will then be reviewed, and an attempt will be made to discuss the metabolism of the body fluids as a whole.

THE METABOLISM OF WATER.

The Water Gontent of the Mammalian Body.

The water content of the mammalian body is estimated to be from 60 to 70 per cent of the total body weight. Harold Skelton (2) has shown that the water content of corresponding organs in different animals under normal conditions is nearly the same and does not vary by more than the figures given by different authors for the organs of man. He estimates the water content of man to be approximately 63 to 65 per cent of the body weight. H.G.Close (3,4,) determined the water content of the various tissues of man. Table I presents his findings.

Group A.		Group B.		Group C.	
Tissue.	% Water.	Tissue.	% Water.	Tissue.	% Water.
Cerebro Spinal Fluid.	99	Grey Matter (Rolandic Area)	85	Articular Cartilage	73
				White Matter.	71.3
Lymph.	95	Lung.	84	Costal Cartilage.	68
Synovial Fluid.	94	Kidney.	82.5	Tendo Achilles.	66.7
Serum.	92	Heart Muscle.	80.3	Red Blood Cell.	66
		Plain Muscle.	80	Connective Tissue.	62
		Suprarenal.	80	Bone.	30
		Spleen.	79	Adipose Tissue.	30
		Pancreas.	79		
		Nerve.	78		
		Liver.	76.9		
		Volunt. Muscle.	76.8		
		Thyroid Gland.	76.3		

He divided the body tissues into three main groups from the point of view of their water content and arrived at certain interesting conclusions. These groups are;

Group A. The body fluids, cerebro-spinal fluid, plasma, synovial fluid etc., whose water content varies from 90 to 99 per cent.

Group B. The nuclear or cellular tissues, grey matter of the central nervous system, glands, muscles etc., whose water content varies from 75 to 85 per cent.

Group C. The anuclear tissues, connective tissue, cartilage,bone, fat etc., whose water content varies from IO to 73 per cent.

The lower limit of group B and the upper limit of group C tend to overlap so that the division between groups B and C is not so clear as that between Groups A and B. But there are important differences between the nuclear and anuclear tissues. The pH of group B tissues is kept constant by buffering, a property anuclear tissues do not appear to posses. There are mainly nucleo-proteins in the group B nuclear tissues and gelatin derivatives in the group C anuclear tissues. Group B tissues with many nuclei contain more water than group C tissues with few nuclei. This relationship of the nucleus to the water content of the cell is seen a striking way in cells which ultimately loose their nucleus. For example, the water content of young nucleated red blood corpuscles is 75 per cent; when mature and anuclear, the red blood cells only contain 65 per cent of water. In nuclear tissues the metabolic rate is much higher than in the supporting anuclear tissues. It seems therefore, that the greater the metabolic rate of a tissue the higher is its water content, a principle which is seen in the process of growing old, where there is a parallel decline both in the water content of the tissues and in their metabolic rate.

While these observations on the water content of the tissues of the body are interesting, there is at the present time insufficient knowledge to allow of more than the most general of deductions therefrom. The metabolism of water must still be discussed therefore with reference to the organis as a whole. The most satisfactory method of considering the physiology of water is to examine under two main heads.(a) The exchanges between the body and its environment, and (b) Its distribution among the tissues.

The Exchange of Water between the Body and its Environment.

In health, the intake and output of water is so adjusted that the one balances the other, and the water content of the body is maintained at a remarkably constant level. This nice adjustment of intake and output is known as water balance and is maintained by the equalisation of intake and output, and departures therefrom induce a state of water imbalance. Naturally, during short periods of time, the intake and output of water are not equal. For instance, after drinking a considerable quantity of fluid the body has temporarily gained water and balance will not be re-established until the excess water has been excreted. During periods of great activity or when the external temperature is high, the body will require more water than periods of inactivity or when the external temperature is low. But, if much fluid id ingested, much will be excreted and conversely, if only a little fluid is required by the organism it is only because only small amounts are being excreted. Water balance therefore in health is maintained by balancing the out put and intake, and is practically independent of the volume of the ingested fluids.

The Paths of Intake.

. Alimentary Ingestion.

Water is normally ingested through the alimentary tract both in the form of fluid and in combination in the food. The mammalian skin can absorb water into its outer layers, but its passage inward, in appreciable amounts, into the body does not occur. The rectal administration of fluid, although of great clinical value is artificial and never takes place normally.

The actual intake of water in fluid form varies from 800 to 2000 c.cs. a day more being drunk during hot weather than during cold. There are also considerable individual variations, mainly the result of habit, and men drink more water than women. It is probable that civilised man drinks too little water, 1500 c.cs. in cold and 3600 c.cs. in hot weather being more nearly the ideal intakes. for adults of normal weight.

The solid constituents of the diet contain, on an average, about 70 per cent of water. It is actually still impossible to give exact figures for the water content of most diets, as it is present in several forms, ranging from pure solvent, through water of crystallisation, of colloidal hydration, and of secondary valance, to water combined with carbon to form carbohydrate and the like. The following table gives the average approximate percentage water content of some common foodstuffs.

TABLE 2.

Apples.	84.I	Cabbage.	92.4	Lamb,roast.	67.I
Artichokes.	79.5	Carrots.	88.2	Leeks.	88.2
Asparagus.	93.0	Cauliflower.	9I.7	Liver,uncooked.	7I.2
Bacon,uncooked	20.2	Lettuce.	94.8	Macaroni, uncooked.	I0.3
Bananas.	74.8	Celery.	93.7		
Beans,raw.	88.9	Chicken,raw.	63.7	Mackerel.	73.4
Beef,lean.	7I.0	Cod,fresh.	82.6	Oatmeal,uncooked	7.7
roast.	48.2	Eggs.	73.7	Onions.	87.5
Bread,white.	35.6	Endive.	93.3	Oranges	87.2
Whole wheat	38.4	Grapes.	8I.6	Peas,fresh.	74.3
Butter.	II.0	Halibut.	75.4	Potatoes.	77.8
Buttermilk.	9I.0	Ham,fresh lean.	60.0	Salmon.	64.3
Milk.	87.0	Beef,heart.	62.6	Tomato.	94.I
Cream,40 %.	54.3	Honey.	I8.2	Veal.	69.0
Cheese,cheddar.	27.4	Kidney,beef.	76.7	Whitefish.	69.8

From an examination of the table one is impressed with the high percentage water content of most foods. Vegetables have an average content of approximately 90 per cent, animal foods of 60 to 75 per cent, and specially prepared cereals such as bread, oatmeal etc., have a water content of from I0 to 35 per cent. In addition, after absorbtion, water is formed when the constituent proteins, fats, and carbohydrates, are oxidised for energy purposes. One gram of protein on oxidation yields 0.4I grams of water, one gram of fat I.07 grams, and one gram of carbohydrate 0.6 grams of water. For clinical purposes, the total water content and the water formed by the complete oxidation of a normal mixed diet may be taken to be equal to 90 per cent of the weight of the diet. Such a diet, on complete absorbtion and oxidation, provides from 250 to 400 c.cs. of water. By this approximation an error of less than 200 c.cs. is introduced into a daily calculation of water balance.

2. Alimentary Absorbtion.

After ingestion, water is absorbed into the body mainly by the small and large intestines, though small amounts may be absorbed by the stomach. It carries with it in solution the products of digestion and electrolytes, both ingested in the food and secreted into the gut in the several digestive juices. The solution absorbed ordinarily has an osmotic pressure nearly equal to that of the blood. If a concentrated solution exists in the gut, to effect the absorbtion of an osmotically equivalent solution to the blood, water is poured into the intestine until the gut contents are approximately isotonic with the blood, after which absorbtion proceeds; and conversely, if water alone be drunk electrolytes are added to it from the gut wall until the resultant solution in the intestines is nearly isotonic, thus again permitting absorbtion. Water is absorbed most quikkly if taken alone, or with food that after digestion forms a solution of lower osmotic pressure than the blood plasma. It is evident,therefore, that it is to the advantage of the body to take adequate amounts of water with food in order rapidly to effect absorbtion both of the food and the water.

Factors Influencing the Rate of Alimentary Absorbtion.

The rate of absorbtion of water is influenced by a large number of factors many of which as yet are only partly understood

I. The Effect of Portal Obstruction.

J.McMichael and F.H.Smirk (5) in a very interesting series of experiments on rats, showed that in the presence of partial portal obstruction, produced by tightning a ligature around the portal vein until slight cyanosis of the gut appeared, the rate of absorbtion of water was considerably reduced; only 30 per cent of the water given was absorbed in 35 minutes instead of 70 per cent as in the controls. In the presence of portal obstruction the diuresis provoked by the administration of water was delayed in its onset, and the rate of excretion was lessened, though the duration of the diuresis was prolonged. This delay in the excretion of urine after the administration of water by mouth has been called opsiuria and is the earliest sign of portal obstruction and long precedes the developement of the classical complex of ascites, splenomegaly, haemorrhoids, gastro-intestinal haemorrhages, and the developement of a collateral circulation in the abdominal wall.

2. The Effect of the Presence of Certain Substances in the Intra-Intestinal Solution.

Certain substances are only absorbed by the intestine with great difficulty. For example, magnesium sulphate extracts water from the blood circulating in the gut wall until a solution isotonic with the blood is produced.This solution thereafter passes on and is excreted in the faeces. Magnesium sulphate therefore, prevents the absorbtion of water from the intestine. J. Rabinovitch (6) has shown:

a. That the absorbtion of both water and chloride from the small intestine is more rapid from a solutioncontaining an excess of potassium ions, and considerably more rapid from a solution containing an excess of calcium ions, than it is from 0.0% sodium chloride solution or from Ringers solution.

b. Acacia has no significant effect on the absorbtion of either water or chloride.

c. Both water and chloride absorbtion is increased after the administration of atropine.

From these examples it will be seen that, in addition to the necessary production of osmotic equilibrium between the blood circulating in the intestinal wall and solution in the intestine,other factors, many of which are as yet unknown, influence the rate of absorbtion of both water and dissolved substances from the gut. A great deal of investigation is still required in this field.

The watery solution of the products of digestion, and electrolytes, both ingested andsecreted in the various digestive juices, having being been reduced approximately to osmotic equilibrium with the blood is then absorbed into the blood stream.

Small amounts of water do not appreciably increase the blood volume because the waterpasses rapidly from the blood to the other extracellular fluids of the body, mainly to the interstitial fluid, and then by osmosis into the cells to augment the intracellular fluids. Any excess of water over the body's needs is raplidly excreted by the kidney.

The absorbtion of large amounts of water e.g., IOOO c.cs. produces a definite fall in the total osmotic pressure of the blood plasma(7). This continues rapidly for 25 to 45 minutes, average 35 minutes, and then more slowly until 35 to 60 minutes, average 45 minutes, after absorbtion. In subjects weighing between 64 and 75 Kg. the average fall lies between I.5 and 2.75 per cent of toal osmotic pressure.

There is at the same time a definite fall both in the concentrations of haemoglobin and serum proteins. The blood volume therefore is definitely increased by the rapid ingestion of large quantities of water.

Normal blood volume is shortly reestablished;

a. By the distribution of the excess water among the other extracellular fluids especially the interstitial fluid.

b. By the transference of water from the interstitial fluid to the cells to equalise the osmotic pressure on either side of the cell membrane.

c. By the excretion through the kidneys of the water ingested in excess of the needs of the body.

The effects of the excessive administration of water will later be discussed when the subject of water intoxication is considered.

<u>The Paths of Output.</u>

While there is normally only one important route by which water is taken into the body, there are several by which it is excreted. Within certain limits these excretory routes may compensate for one another.

The paths of water excretion are:

I. Through the kidneys.

2. Through the lungs.

3. Through the skin.

4. Through the alimentary tract.

5. Special paths of excretion.

   a. The tears.

   b. Nasal secretions.

   c. Spitting and drooling.

   d. Haemorrhage.

e. Rupture of skin vesicles and blisters.

f. Secretions of the genital tract.

g. Evaporation from exposed tissues during operations, drainage from fistulae.etc.

The first four are normally the important paths of water loss and will be discussed in some detail. The special paths whereby fluid may be lost will only be noticed when the clinical implications of water balance are being reviewed.

I. The Urinary System.

The kidneys have certain very impottant functions in relation to the maintenance of normal water balance. They strive continually to maintain the normal total osmotic pressure and pH of the body fluids at certain optimal constant values. In addition they have the important function of excreting certain soluble waste products of body metabolism such as urea, uric acid, creatinine etc. By their extraordinary flexibility if function they can excrete large volumes of dilute urine when the intake of water has been excessive, or small volumes of concentrated urine when the water intake has been minimal, thus promoting the maintenance of the normal total osmotic pressure of the body fluids. If electrolytes such as sodium chloride have been taken in large amounts the excess over the body's needs is excreted in the urine. When on the other hand, the body electrolytes have been depleted with a consequent reduction in the total osmotic pressure of the body fluids, the kidneys retain osmotically effective substances,such as urea, to prevent an excessive fall in the total osmotic pressure of the body fluids as a whole. This function is well illustrated in Case 4 of the sodium chloride depletion experiments, in which, in spite of a large urinary output, there was a gradual rise in the concentration of urea in the blood. It must be emphasised that this retention of urea has no effect on the partition of water between the intracellular and extracellular fluids because urea passes freely from one side of the cell membrane to the other. Urea merely raises the total osmotis pressure of the body fluids as a whole. The kidneys in addition to their function of regulating the water and salt content of the body fluids in order that the optimal total osmotic pressure of these fluids may be maintained, exert an important effect on the Acid Base balance of the body. This is effected mainly in two ways:

. The Acid Phosphate / Alkaline Phosphate Mechanism.

If there be a tendency to alkalosis alkaline sodium phosphate Na_2HPO_4 is excreted in the urine, and basic substances are thus eliminated. If on the other hand, there be a tendency to acidosis acid sodium phosphate NaH_2PO_4 is excreted in the urine thus eliminating from the body the excess of acid over alkaline radicals.

. The Ammonium Mechanism.

The epithelium of the renal tubules has the power of manufacturing NH_3 and passing it into the blood stream where it becomes available for neutralising ~~acid~~ acid radicals to form ammonium salts which are subsequently excreted in the urine, thus sparing the fixed base of the plasma. In acidosis the kidneys makes more NH_3 to deal with excess acid radicals present; in alkalosis, as ample base is already available the kidney makes less NH_3 or none at all.But in spite of the great range of action possesed by the kidneys there are limits which cannot be transgressed. This is particularly true of the water requirements necessary to excrete the waste products of metabolism which are eliminated in the urine. It will be seen later that the water lost from the skin and lungs has the all important function of regulating and maintaining body temperature within narrow limits. In the presence of dehydration, all other methods of water elimination have long ceased to be operative before there is any significant reduction in the loss of water through the skin and lungs. Thus urinary excretion in severe dehydration ceases and the kidney can no longer influence the acid base balance of the body through the acid phosphate- alkaline phosphate mechanism. The waste products therefore, requiring elimination in the uri ne are retained and accumulate in the body fluids, as is shown by a rise in the blood non-protein nitrogen, and considerable departures from the hormal alkali reserve.

Lashmet and Newburgh (8), assuming that 35 grams of solids are excreted daily in the urine, calculated the minimum volume necessary per day to effect the excretion of this weight of urinary waste products, both for normal and diseased kidneys. Their findings are given in Table 3.

TABLE 3.

Kidneys.	Maximum Concentrating Ability. Specific Gravity.	Minimum Volume of Water Required to Excrete 35 Gr. Urinary Waste Products.
Normal.	I032 - I029	473
Diseased.	I028 - I025	595
	I024 - I020	605
	I0I9 - I0I5	850
	I0I4 - I0I0	I439

The volumes given in this table are those necessary for the excretion of 35 grams of waste materials by both healthy and diseased kidneys under conditions forcing them to work at their maximum concentrating ability. My own researches indicate that during the post-operative period many patients excrete considerably more than 35 grams of waste materials in the urine. In a series of ten subjects whose water balances were studied during the post-operative period one excreted a maximum of 62.3 grams of waste materials in his urineon the first post-operative day. Six excreted more than 50 grams a day during the first three dayas after operation. And the average daily excretion of waste materials in all ten exceded 47 grams. These figures are the more significant when it is realised that all were dehydrated, and had definite elevations of blood non-protein nitrogen during the three post-operative days studied.

It therefore follows that the minimum volume of water necessary to excrete the urinary waste products may be nearly double the volume given above byp Lashmet and Newburgh. As a clinical rule it can be stated that patients with healthy kidneys in the post-operative period should be supplied with sufficient water to permit of the daily excretion of I500 c.cs. of urine.

The Loss of Water through the Lungs.

The rate of water loss from the lungs and nasopharyngeal passages varies with the humidity of the inspired air. Expired air is ordinarily saturated with water at about 34.C. and therefore it carries away with it as much water as is necessary completely to saturate it at this temperature. Under basal conditions in adults, the pulmonary loss averages 36% of the extra-renal losses, or about 300 c.cs. in 24 hours.(9). It increases measurably with such activities as reading aloud and singing, and very considerably when the respiratory minute volume is much increased by any condition such as exercise or other acidosis, and in diseases such as pneumonia.

The Loss of Water through the Skin.

The loss of water from the skin is due partly to sweating and partly to the evaporation of water passing by osmosis through the skin. Sweating,under basal conditions, is commonly absent in temperate or cold climates, in which case "insensible perspiration" is entirely independent of sweating. In certain emotional states, if the external temperature is high, and especially if the humidity of the atmosphere also is high, the loss of water from the skin becomes markedly increased by sweating and visible water appears on the skin. Great physical activity also causes considerable loss of water through the skin. In conditions in which the loss of water through the skin is mainly the result of the evaporation of water which has passed by osmosis through the skin, only small amounts of electrolyte are lost, mainly sodium and potassium chlorides, apparently principally derived from the epidermis itself or from sebaceous secretion. As the loss of water becomes greater, a greater and greater proportion of the loss is due to true sweating. At the same time the proportion of electrolytes lost tends to increase. Under extreme conditions of work, temperature and humidity, when the intake of water is unlimited such losses of electrolytes in the sweat may profoundly affect the electrolytic content of the body. Although electrolytes thus are lost in the insensible perspiration and in the sweat, such losses are purely incidental, because all body secretions contain electrolytes. These losses of electrolytes from the skin normally serve no physiological purpose. The function of the insensible perspiration, the sweat, and the water loss from the lungs, is pre-eminently to maintain the constancy of the body temperature.

Insensible Loss of Water.

The loss of water in the expired air, and from the skin in the insensible perspiration and sweat, is called the Insensible Loss of Water. Investigations into the functions which it subserves have been very numerous and many publications are devoted to their consideration. Among the more important are those of Newburgh and his associates (IO,II,I2,I3,), Benedict and Root (I4), Heller and Schwarz (I5), Levine and his associates (I6,I7), Lavietes (I8), and Ginandes and Topper (I9,20). for the purposes of this paper full discussion of the subject is not required; only the functions of the insensible loss of water will be considered.

If the mean temperature of the body is to remain constant heat elimination must equal heat production. The elimination of heat is effected by the following methods:

a. Radiation from the body surface and lungs.
b. Conduction between the body and its surroundings.
c. Vaporisation of water from the body surface and from the lungs.
d. Small amounts of heat are lost by the body in the urine and stool.

By radiation and conduction, under normal conditions of temperature, approximately 75% of the total heat production is dissipated. The amount so lost naturally decreases withelevation of the temperature of the surroundings, until, if it reach 98 F. almost none is lost by these methods.

The vaporisation of water constitutes the flexible method by which heat may be eliminated.When Ic.c. of water is vaporised by the body it carries away with it 0.58 large calories,and,under conditions of activity which do not produce visible sweating approximately 25% of the body heat is dissipated by the vaporisation of water. Under the above conditions of activity this approximation is sufficiently accurate to allow of the estimation of the body's heat production from the determination of the insensible loss of water. Numerous correlations also have been made between the insensible loss of water and body weight, sitting height, and standing height etc., of the body. Suffice it to say that for normal individuals both children and adults, doing light work without visible sweating, the amount of heat lost by vaporisation is 25% of the tptal heat production of the body. Thus under these conditions of activity in an adult whose heat production is 2400 calories per day, I034.5 c.cs. of water will have to be vaporised from the lungs and skin to eliminate 25% of this total heat production or 600 calories.

The amount of heat lost by radiation and conduction decreases when the external temperature rises and it approaches zero at approximately 98 F. In order therefore to dissipate body heat an increased demand will be made on the process of vaporisation. This demand is met by increasing the rate of respiration and the volume of perspiration secreted. If the humidity of the surrounding atmosphere is very high, the rate of evaporation of the perspiration so produced will be markedly reduced, and much will appear as water on the surface of the body, thus reducing the efficiency of this method of heat elimination. If this method of heat dissipation fail under conditions of high external temperature and humidity, the body temperature will rise rapidly and the subject will pass into heat stroke. The vaporisation of water from the lungs and skin is therefore concerned with the regulation of the body temperature. Homiothermal organisms maintain a very constant temperature and departures therefrom may be prejudicial or even fatal, therefore temperature regulation is of the first importance to these organisms. Since the vaporisation of water is the flexible means of increasing or decreasing heat loss from the body, it has priority over all other methods of excreting water. Inded, it had been shown (I3,2I) that the body may be dehydrated of 6% of its water before any reduction takes place in the amount of water vaporised from the skin and lungs; this degree of dehydration is accompanied by oliguria or anuria. Dehydration exceeding 6% of the total body water lowers the rate of vaporisation and therefore heat loss from the body and is accompanied by a rise in temperature.

Under basal conditions the ingestion of large volumes of water, or of 1% sodium chloride solution does not affect the rate of water vaporisation (21). It may be concluded therefore that the vaporisation of water is not primarily a means of regulating the water content of the body. It subserves heat regulation and has first call on any water available for excretion.

In diseased states which are accompanied by a rise in temperature, in hyperthyroidism, during the recovery period fromoperations etc., the volume of water vaporised may be very considerable. In my series of water balance studies the highest insensible loss of water observed was 2377 c.cs. on the first post-operative day in a case operated on for carcinoma of the stomach. Maddock and Coller have recorded vaporisation losses of 2470 c.cs. in one day in a case of intestinal obstruction, 2062 c.cs. in a case of exophthalmic goitre, and 2729 c.cs. in a case of lung abcess drained by rib resection (22,23).

Water vaporisation therefore constitutes an important means by which the body looses fluid. Its clinical implications will be discussed more fully when the practical applications of water metabolism are considered.

4. <u>The Water Losses from the Gastro-Intestinal Tract.</u>

Water is actively secreted into the gastro-intestinal tract both in the digestive juices and into the colon with substances such as calcium and sulphates which are largely excreted through this channel. As will be detailed later the volume of the digestive juices is about 8000 c.cs. per day. If, for any reason, these be largely lost in vomitus, diarrhoea, or from an intestinal fistula the body becomes rapidly depleted both of water and of electrolytes which such digestive juices contain. Normally the loss of water in the faeces is from 60 to 150 c.cs. daily and does not exceed 200 c.cs. Normally therefore, the loss of water from the gastro-intestinal tract is insignificant.

5. Special Paths of Excretion.

Water losses through these channels normally do not occur except for the very small volume of the lachrimal secretions which are evaporated from the surface of the eyes. However, these special paths of water loss may become extremely important in diseased states and of themselves cause dehydration.

The Partition of Outputs.

It has been seen that if there be a certain quantity of water available for excretory purposes, the process of vaporisation exercises pre-emptive rights over this water, and, until it has withdrawn its quota, the other excretory functions remain in abeyance. If there be more water in the body than is necessary for vaporisation, then the kidneys excrete the excess, leaving the body in water balance, the faeces normally removing only minimal quantities. If water be lost from the body through other channels, such as by vomiting or in diarrhoeal stools, the body still vaporises water normally until it has lost a weight of water equal to 6% of the total body weight. The secretion of urine has usually ceased when the body is so considerably dehydrated. There is thus no true partition of outputs; the water of vaporisation has first call on all the water available for excretion, and the kidneys are allowed what is left.

B. The Distribution of Water in the Body.

The distribution of water between the various compartments of the body has been, in recent years, the subject of a great deal of research. A complete knowledge of this aspect of water metabolism is of fundamental importance, both from a purely theoretical point of view and also clinically; although a great deal is already known, much remains to be discovered.

One of the first papers dealing with this aspect of water metabolism is that of A.J.Schechter (24). He investigated the qualitative and quantitative changes which take place in certain fluids when injected into the peritoneal cavity of dogs. Three different isotonic fluids were used:

I. Physiological saline (0.9% sodium chloride in distilled water).

2. Isotonic glucose solution, (5% glucose in distilled water).

3. A salt bicarbonate solution, Darrow-Cunninghams solution, which was made up as follows: To 500 c.cs. of sterilised 0.II N HCl (containing 0.I86 Gm. of KCl per liter) were added 5.9 Gm. of $NaHCO_3$ powder previously sterilised by dry heat. The mixture was shaken for five minutes and then injected. It should then contain approximately I40 m.Eq. of Na^+, II0 of Cl, 30 of HCO_3, and 5 of KCl.

500 c.cs. of each solution at a temperature of 38 C. was injected into the peritoneal cavity of separate dogs. At varying times after the injection, samples of the fluid in the peritoneal cavity were removed for analysis.

To study the volumetric changes in these solutions, 25 c.cs. of each was injected into the peritoneal cavities of guinea pigs, and at varying times thereafter the animals were sacrificed and all available fluid in the peritoneal cavity was removed and measured.

These interesting experiments gave the following results:

I. The electrolyte composition of the injected fluid became altered and tended to approach the composition of interstitial fluid. That is, these injected isotonic solutions were not in chemical equilibrium with the blood plasma; they underwent changes in chemical composition until chemical equilibrium was reached with the plasma, while the isotonicity of the solution remained unimpaired. It was found that the total base of the injected fluid remained practically unaltered, but the chemical pattern of the acidic ions altered radically, though remaining equivalent chemically to the total base. In the case of sodium chloride injections the chloride concentration fell, but concurrently, bicarbonate and organic anions were added to the solution, thus preserving the constancy of the equality between the basic and acidic ions.

2. Isotonic sodium chloride and sodium chloride/sodium bicarbonate solutions were absorbed from the peritoneal cavity at constant rates, which were almost identical.

3. In the case of the glucose injections, there was initially a marked rise in the volume of the fluid in the peritoneal cavity. At the same time electrolytes were added to the fluid and the concentration of glucose gradually fell. When it had fallen considerably, absorbtion proceeded at approximately a constant rate. It was noticed that, during the period in which the peritoneal fluid had greatly increased in volume, the animals were dehydrated. The explanation for the increase in volume of the peritoneal fluid after glucose injections is supplied by Clark (25), who points out that the electrolytes which enter the peritoneal cavity with fluid to adjust the chemical equilibrium do so more rapidly than the large, slowly moving glucose molecules can carry it out.

This experiment is of particular importance to the present discussion, because it provokes a shift in body water from one compartment to another without alteration in the total water content of the body.

Similar experiments were undertaken by Schechter, Cary, Carpentieri and Darrow (26), and comparable results were obtained. That is, when a watery solution was placed in the peritoneal cavity, it tended to assume the composition of a fluid in ionic and osmotic equilibrium with blood plasma. When 5% glucose solution was injected, it also was observed that, while the volume of the solution in the peritoneal cavity increased at first, at the end of from four to six hours sufficient absorbtionhad taken place to restore it approximately to that of the fluid injected. This observation is of the first importance because, since the fluid in the peritoneal cavity was not immediately available throughout the tissues, the body may be considered to have lost temporarily the amount of electrolyte which had passed into the fluid in the peritoneal cavity, while the total amount of body water remained relatively unaltered. In addition, during the experiments with 5% glucose solution, there was anuria, and therefore, the only loss of water was by evaporation and the only gain was from cellular oxidations. Over the short period of time of the experiment, this gain and loss of water can be considered to be equal and can therefore be neglected.

A further series of experiments were undertaken by Darrow and Yannet (27) with the express purpose of investigating the changes which occur throughout the body when extracellular electrolyte was both temporarily increased and decreased without alteration in the total amount of body water. The injection of 5% glucose solution into the peritoneal cavity has been shown to effect such a decrease in extracellular electrolyte without alteration in the total amount of body water at the end of four hours. These authors also injected saline of double physiological strength (I.8% sodium chloride solution) into the peritoneal cavity, and found that, after about four hours, the fluid in the peritoneal cavity was in approximate ionic and osmotic equilibrium with the blood plasma, and that the volume recovered was approximately the same as that injected. Therefore the total amount of extra-cellular electrolyte was increased without any significant change in the volume of total body water.

Healthy dogs, rabbits, and monkeys (Macasus rhesus), were used and two procedures were adopted. A preliminary blood specimen was taken and immediately transferred to a tube containing mercury with special precautions to prevent any change in the degree of oxygenation.

Procedure I. Approximately IOO c.cs. of sterile 5% glucose solution per Kgm. of body weight was injected into the peritoneal cavities of the first series of animals.

Procedure 2. The same amount of sterile I.8% solution of sodium chloride was also injected intra-peritoneally into a second series of animals.
Both solutions before injection were warmed to 38 C. All the urine was collected and four to six hours later a second specimen of blood was obtained and treated in the same way as the first specimen. At the same time a sample of peritoneal fluid was obtained. To determine the amount of fluid remaining in the peritoneal cavity after approximate equilibrium had been established, fourteen animals were sacrificed and the peritoneal fluid drained and measured. These animals were also examined for gross pathological changes.

The results of these experiments are so important that the following is very largely a rearrangement of the authors paper in order to emphasise aspects pertinent to this discussion.

As a result of procedure I in which 5% glucose solution was injected into the peritoneal cavity the following effects were observed.

I. There were no local signs of pain or peritoneal irritation.

2. All the animals (8 dogs, 5 rabbits, and 5 monkeys) showed signs of mild to severe dehydration comparable to those observed in dehydrated patients. The tongue and mucous membranes were dry; the skin showed loss of turgor; the animals became languid and looked sick. In the rabbits and monkeys greyish pallor, such as is seen in "alimentary toxaemia" could be distinguished. In about 24 hours the animals recovered completely.

3. No urine was passed by the animals during the duration of the experiment.

4. In view of the clinical evidences of dehydrationit is interestin to note that the animals were not thirsty.

5. In the animals sacrificed, the change in the total amount of peritoneal fluid amounted to an increase or decrease of less than I0% of the amount injected. Since the amount injected was I0% of the body weight, and since the total body water is about 70% of the body weight, the experiment would change the available body water by less than I.5%. Because blood plasma, interstitial fluid, and intracellular fluid are all in osmotic equilibrium, the effect of this change in body water will be distributed throughout all the body fluids and will be of minor importance in explaining changes found in the blood. In other words, the chief changes produced by the "glucose" experiments, are brought about by the withdrawal of extracellular electrolyte. The amount of chloride so lost was about 25% of the total body chloride, and the sodium about 20% of the total body sodium.

6. Changes in the Blood.

The red blood cell count and the concentration of serum proteins were increased. Roughly, by calculation the diminution of plasma volume which would cause such increases in the concentration of red blood cells and serum proteins varied from 8 to 27% of the original plasma volume.

7. The concentration of cell proteins in the red blood cells decreased. The volume of intracellular water was therefore increased. this increase in intracellular water amounted to I.4 to 7.3% of the original cellular water. Since the total body water had changed relatively little, this increase in cellular water was presumably derived from the extracellular water.
8. In all cases considerable reductions were found in the concentration of chloride and sodium in the serum. It is obvious that these reductions were chiefly brought about by the migration of sodium and chlorine into the peritoneal cavity.

As the result of procedure 2 in which I.8% sodium chloride solution was injected into the peritoneal cavity the following effects were observed.

I. There were no local signs of pain or peritoneal irritation.
2. Few clinical signs were produced. The animals retained their appetite and did not look ill. They became thirsty but no loss of skin turgor occurred.
3. In three of the experiments on dogs a definite diuresis occurred resulting in a loss of about 25% of the fluid injected, and the urine passed contained 200 to 350 m.Eq. of sodium and chloride per liter. In the other experiments practically no urine was passed in the 4 to 6 hours.
4. In the animals sacrificed the increase or decrease in the volume of the peritoneal fluid recovered was also less than I0% of the amount injected. The effects on the total volume of the body fluids presumably were the same as those discussed in the "glucose" experiments. That is, there was a change in the available body water of less than I.5%. Neglecting excretion in the urine, which was negligible in most of the experiments, body chlorides were increased by about 50% of the total body chloride and body sodium by about 30%.
5. Changes in the Blood.

The red blood cell count and the concentration of serum protein were decreased. The apparent increases in plasma volume were I6 to 52% when calculated from the changes in the proportion of red cells in the blood, while tha apparent increases were 4 to 24% when calculated from the changes in the concentrations of serum proteins. Many factors influence the concentration, both of the serum proteins and of the red blood cell count, but the changes were sufficiently great to indicate that considerable increases in plasma volume had occurred.

6. The concentration of cell proteins in the red blood ceels increased owing to losses of erythrocyte water. the losses of cellular water varied from 2 to 7% of the original water in the cells. Because body water remained relatively constant, the water which left the red cells presumably migrated to the extracellular water.

7. In all cases considerable increases in the concentration of chloride and sodium in the serum occurred owing to the migration of these ions from the fluid injected into the peritoneal cavity.

Discussion and Conclusions.

Almost seven tenths of the body is made up of water which moves between the intracellular and extracellular spaces in such a manner as to maintain osmotic equilibrium between the fluids of the cells and that in the extracellular spaces. since about nine tenths of the osmotic pressure of the body fluids is maintained by electrolytes, the distribution of body water is largely determined by the distribution of electrolytes. Fuethermore, as the concentratiom of anions equals the comcentration of cations, the approximate osmotic relations are given by the concentration of total base in milliequivalents per liter of water. Because the preponderant bases are the univalent ions, sodium and potassium, the concentration of these cations determines roughly the osmotic pressure. One may therefore surmise that the factors controlling the distribution of sodium and potassium also goverm the distribution of water.

From analyses of blood plasma, lymph, oedema fluid, and cerebro spinal fluid it is fairly well established that all extracellular fluids have approximately the composition of plasma, except that little protein is present in the extracellular fluids outside the vascular system. The actual amount of extracellular fluid is unknown, but analyses of muscles (28) and whole bodies (29,30) suggest that about

20% of the body weight must be due to extracellular fluid. Therefore about 50% of the body weight is made up of intracellular water.

It is believed that in the intracellular fluids the chief anions are proteins and phosphates, and the chief cation potassium. the distribution of sodium and chloride on one side of the cell membrane and potassium and phosphate on the other indicates that the cell membrane is relatively impervious to these ions. It follows therefore that there is no great variation in the quantity of intracellular electrolyte, and,to maintain osmotic equilibrium between the intracellular fluid containing a fixed amount of electrolyte and the extracellular fluid containing variable amounts of electrolyte, the volume of the intracellular water and therefore the concentration of intracellular electrolyte must vary. This variation is accomplished by the transference of water from one side of the cell membrane to the other. Thus osmotic equilibrium is maintained between the intracellular fluids and extracellular fluids by water transference across the cell membrane.

In the experiments which have just been described this transference of water across the cell membrane is well illustrated. In the "glucose" experiments the incteases in the concentration of proteins in the serum and of red cells in the blood indicate that the plasma had been reduced by from I8 to 49% of its original volume. Analysing this reduction of plasma volume the follwing deductions are admissable:

I. Extracellular electrolyte, sodium chloride, had been reduced by approximately 20 to 25% by the passage of sodium chloride into the fluid in the peritoneal cavity where it was temporarily removed from the available extracellular fluid.

2. As a result of the loss of electrolyte, especially the cation sodium, the osmotic pressure of the extracellular fluids was reduced.

3. Since apparently neither sodium or potassium can pass through the cell membrane, to restore equality between the osmotic pressures of the intracellular and extracellular fluids, water must pass from the extracellular fluids into the cells, until the osmotic pressures of the two fluids are again equal.

4. As the result of the loss of extracellular electrolyte and the redistribution of body water without change in its volume, the total osmotic pressure of the body fluids was reduced by the osmotic pressure which would be exerted by the amount of electrolyte lost in a volume of fluid equal to the toal volume of the body fluid.

5. Thus the intracellular fluids have gained and the extracellular fluids have lost water. If the extracellular water is 20% of the body weight and the intracellular water is approximately 50%, then if 25% of the extracellular water passes into the cells the intracellular water will be increased in volume by about I0%.

From all the above it may be reasoned that, with a given loss of extracellular electrolyte accompanied by a disproportionate loss of water, or, as in the "glucose" experiments by little change in body water, the magnitude of the reduction in extracellular electrolyte will be dependent, not on the volume of the extracellular fluid but rather on the total volume of the total body water.* This deduction follows from the fact that the changes in osmotic pressure produced by loss of extracellular electrolyte must be equalised throughout all the body fluids. Since this adjustment takes place chiefly by shift of water from the extracellular to the intracellular compartments, the magnitude of this transfer of water will be dependent upon the relation of the volume of extracellular water to the total body water. It is, therefore, apparent that a value for the proportion of the body fluid in the extracellular spaces is a necessary factor for the prediction of alterations in

* This relationship for constant total body water when the only loss of base is loss of sodium from the extracellular water, may be expressed by the following formula:

$$(Na)_I V - (Na)_p = (Na)_2 V.$$

Where $(Na)_I$ is the original concentration of sodium in serum water: $(Na)_2$ is the second concentration of sodium in serum water; $(Na)_p$ is the change in body sodium and V is the volume of body water in liters. By applying this formila to the data of the "glucose eaperiments, Darrow and Yannet found that it gave the weight of the total body water to be approximately 70% of the total body weight which agrees with previous estimations by other methods.

the distribution of body water under varying conditions.

The observations in the saline experiments fit in with the concepts propounded above. Since, in these experiments, extracellular electrolyte was increased, the shift in body water was from the intracellular to the extracellular compartments. That is, there was hydration of the extracellular fluids and dehydration of intracellular.

It is instructive to recall at this point the clinical effects produced by these experiments. The only symptom or sign produced by the dehydration of the intracellular fluids was thirst. The symptoms and signs, on the other hand, of dehydration of the extracellular fluids were those which occur clinically in dehydrated patients with the single exception that thirst was absent. Clinical dehydration therefore is associated with loss of water from both the extracellular and intracellular fluids; the loss from the extracellular fluids acconting for the loss of turgor, dryness of the tongue and mucous membranes, etc., and the loss of water from the cells accounting for the sensation of thirst which thus is apparently a cellular phenomenon.

It has recently been shown by Gilman (31) that a decrease in blood pressure and an increase in susceptibility to the effects of haemorrhage occurs with loss of extracellular electrolyte with little change in total body water. Also that disturbances in the distribution as well as in the amount of body water probably occur as the result of disproportionate losses of water and electrolyte in diabetic coma, persistent vomiting, diarrhoea, heat stroke,etc., Thus the partition of water between the intracellular and extracellular compartments of the body is of great clinical importance, and one looks forward with eagerness to the day when, not only, as is now possible, can one be assured of the proper total hydration of a patient, but also can be certain that the body water is ideally distributed between the cells and extracellular spaces.

Progress in this direction has recently been made by Harrison, Darrow, and

Yannet (32), who have developed a system for calculating the volumes of the intracellular and extracellular fluids of the body. They point out that accurate information concerning both intracellular and extracellular fluids is limited to the concentrations of electrolytes in extracellular fluids,and that the concentrations of electrolytes in various extracellular fluids are closely predicted from the concentrations in venous serum. But, if the total amount of an ion present only in extracellular water were known, then the volume of the extracellular water could be computed from the concentration of that ion in the extracellular fluid. They applied these concepts to analyses of whole animals and organs, together with analyses of venous serum, and calculated the total amounts of both extracellular and intracellular water. They used dogs, monkeys, and rabbits and assumed that in these animals the chloride ion is confined to the extracellular water. This assumption is probably not true for man, but in these animals assuming the correctness of this major premise,and that the Donnan factor for estimating the concentrations of sodium, potassium, and chloride in extracellular fluid was 0.96 it follws that:

I. Total extracellular water equals total chloride divided by the concentration of chloride in extracellular water.
2. Intracellular water equals the difference between total water and extracellular water.
3. Extracellular sodium equals the product of the volume of extracellular water and the concentration of sodium in extracellular water.
4. The sodium not present in the extracellular water equals the difference between the total sodium and the extracellular sodium.

Many other ions can be calculated on similar principles.By applying these principles the authors found that the extracellular water composed about 27% of the body weight and the intracellular water varied from 29 to 45%, being lower in fat animals.

Other authors applying the same principles have reported similar results. Crandell and Anderson (33) estimated the amount of water available for the solution of injected sodium thiocyanate from the concentration of thiocyanate ion in the serum and the quantity of thiosyanate ion retained. In man, the water available for solution of thiocyanate ion was from 20 to 25% of the body weight. Lavietes, Bourdillon, and Peters (34) repeated these experiments on humans and used sucrose in a similar manner, and, in both types of experiments their values agreed with those of Crandall and Anderson and they suggested that the water volume involved in these experiments represented the extracellular fluid. From the clinical point of view the determination of the volume of extracellular fluid by the injection of glucose and applying the principles enunciated by Harrison, Darrow and Yannet offers a fertile field for further investigation.

CHAPTER 2.

THE DETERMINATION OF WATER BALANCE.

It now becomes possible to discuss the methods by which water balance may be determined. There are two main methods of investigating water exchange.

1. The Direct Method.
2. The Indirect Methods.

The Direct Method.

This method at the present time is the one usually adopted for the investigation of water exchange in normal and abnormal subjects. It is essentially a gravimetric method and it requires a knowledge of the following.

1. The accurate weight of the subject under standard conditions of nudity, after emptying the bladder, and at the same time every day, or at the beginning and end of the period under investigation.
2. The Weight of the Intake of:
   - A. Fluid constituents of the diet.
     - I. Water content.
     - 2. Solid content.
       - a. Water combined with solids.
       - b. The protein content.
       - c. The fat content.
       - d. The carbohydrate content.
       - e. Other solids such as electrolytes, unabsorbable residue etc.
   - B. Solid constituents of the diet.
     - I. Water content.
     - 2. Solid content.
       - a. The protein content.
       - b. The fat content.
       - c. The carbohydrate content.
       - d. Other solids such as electrolytes, unabsorbable residue etc.

3. The Respiratory Exchanges of the Subject.

The accurate determination of water balance requires a complete knowledge of the energy exchanges of the subject. Therefore the composition of the inspired and expired air should be frequently ascertained during the period under investigation. Ideally, patients and experimental subjects should be enclosed in a respiration chamber which allows of the continuous estimation, over long periods, of the oxygen intake and carbondioxide output. Newburgh, by the use of such a respiration chamber, has greatly developed this aspect of metabolic investigation in relation to water exchange. Knowing the oxygen intake and the carbondioxide output, and therefore the Respiratory Quotient, the heat production of the subject can be estimated. If the protein intake and the nitrogenous excretion of the subject also be known, the amount of protein, fat and carbohydrate which have been metabolised in order to produce the known amount of heat can also be calculated.(35). From the accurate knowledge of the composition of the diet, and consequently its energy value, the calorie balance of the subject will be known. If the heat production of the subject exceed the calorific value of the diet when completely absorbed, then the subject will burn body tissue. If, on the other hand, the heat production of the subject be less than the calorific value of the diet when completely absorbed, then the body will store most of the excess of the intake over the output mainly in the form either of glycogen or fat. This storage will require water in definite amount depending on the nature of the substance stored, and the water so used is not available for the purposes of excretion until the stored substance is metabolised to provide energy for the body.

4. The Weight of the Output of:

A. The Urine.

a. The water content.

b. The solid content of the urine(urea, uric acid, etc.)

B. The faeces.

a. The water content.

b. The solid content, which will include the unabsorbable residue of the diet, substances excreted into the colon such as calcium, sulphate, etc., and variable amounts fat,protein, and carbohydrate from the diet.

C. Losses from Vomitus, Fistulae etc.

a. Water content

b. Solid content. Protein, fat, carbohydrate etc.

D. The Water loss from the Skin and Lungs. Small amounts of electrolyte also are excreted by the skin, but not usually in sufficient quantity as to require determination.

From the above if it be assumed that the calorific value of the diet equals the heat production of the subject and that the diet is completely absorbed, then the components of the water exchange may be expressed by Table 4.

TABLE 4.

Available Water.	Excreted Water.
I. Water of fluids drunk.	I. Water of urine.
2. Water content of the diet.	2. Water of faeces.
3. Water of oxidation of the diet.	3. Water vaporised.
	4. Water in other excretions.

If the calorific value of the absorbed diet be less than the heat production of the subject, then the components of the water exchange may be expressed by Table 5.

TABLE 5.

Available Water.	Excreted Water.
I. Water of fluids drunk.	I. Water of urine.
2. Water content of diet.	2. Water of faeces.
3. Water of oxidation.	3. Water vaporised.
a. Of diet.	4. Water in other excretions.
b. Of body tissue metabolised	

If the calorific value of the absorbed diet be greater than the heat production of the subject, then the components of the water exchange may be expressed by Table 6.

TABLE 6.

Available Water.	Excreted Water.
I. Water of fluids drunk.	I. Water of urine.
2. Water content of diet.	2. Water of faeces.
3. Water of oxidation of such of the diet as is necessary for energy purposes.	3. Water vaporised.
	4. Water used to form body tissue by the excess of the diet absorbed.

The total exchanges of water, solids, and gasses of a subject under investigation may be expressed by the following equation.

$$\text{Change in Weight} = \text{Intake.} \begin{matrix} \text{a. Solids.} \\ \text{b. Water.} \\ \text{c. Oxygen.} \end{matrix} - \text{Output.} \begin{matrix} \text{a. Solids.} \\ \text{b. Water.} \\ \text{c. Carbon dioxide.} \end{matrix}$$

The output of water may be divided into:

A. The water lost in the urine, in the faeces, in vomitus etc., all of which is visible and therefore can be measured directly. These losses are known as The Visible Water Loss

B. The water lost in the breath and perspiration. Only the water lost in the breath can be measured directly by passing the expired air through some intensely hygroscopic substance and weighing this at the beginning and end of the period of study. The gain in weight of the hygroscopic substance will be equal to the weight of the expired water. The sum of the water excreted in the breath and from the skin is knowm as the Insensible Water Loss. The insensible water loss and the respiratory exchange of oxygen and carbondioxide is known as the Insensible Loss of Weight. Insensible Loss of Weight may be expressed by the equation:

$$\text{Insensible Loss of Weight} = \text{Insensible Loss of Water} + CO_2 - O_2$$

Insensible loss of weight will vary therefore with the Respiratory Quotient. Newburgh Wiley, and Johnston (36) have emphasised the important distinction between the Insensible Loss of Weight and Insensible Loss of Water, and give the following interesting table showing the differences between the two for various Respiratory Quotients in cases theoretically losing the same weight og water in 24 hour periods.

TABLE 7.

With R.Q.	Insensible Loss of Water Grs./ 24 Hrs.	Insensible Loss of Weight Grs./ 24 Hrs.
I.00	978	II93
0.82	978	I054
0.707	978	940

From an examination of this table it will be seen that a very real potential exists if the difference between Insensible Loss of Weight and Insensible Loss of Water is not appreciated. In very accurate determinations of water exchange this difference is allowed for. Clinically, however, it is uaual to assume that the Insensible Loss of Weight is equal to the Insensible Loss of Water.

The equation for the total exchanges of a subject under investigation may therefore be restated as follows:

$$\text{Change in Weight} = \text{Intake} \begin{array}{l} \text{a. Solids.} \\ \text{b. Water.} \\ \text{c. Oxygen.} \end{array} - \text{Output} \begin{array}{l} \text{a. Solids.} \\ \text{b. Water. (Visible and Insensible)} \\ \text{c. Carbon dioxide.} \end{array}$$

Substituting Insensible Loss of Weight for Insensible Loss of Water $+ CO_2 - O_2$ the equation will read:

$$\text{Change in Weight} = \text{Intake.} \begin{array}{l} \text{a. Solids.} \\ \\ \text{b. Water.} \end{array} - \text{Output.} \begin{array}{l} \text{a. Solids.} \\ \text{b. Visible Water.} \\ \text{c. Insensible Loss of Weight.} \end{array}$$

Assuming Insensible Loss of Weight = Insensible Loss of Water the equation will now read:

$$\text{Change in Weight} = \text{Intake.} \begin{array}{l} \text{a. Water} \\ \\ \text{b. Solids.} \end{array} - \text{Output.} \begin{array}{l} \text{a. Visible Water.} \\ \text{b. Insensible Water.} \\ \text{c. Solids.} \end{array}$$

Solving for Insensible Water Loss the equation may be expressed:

$$\text{Insensible Water Loss} = \text{Intake.} \begin{array}{l} \text{a. Water.} \\ \text{b. Solids.} \end{array} - \text{Output.} \begin{array}{l} \text{a. Visible Water.} \\ \text{b. Solids.} \end{array} - \text{Change in Weight}$$

From all the above water balance may be expressed by the following equation.

Water Balance =	Available Water.	a. In fluids drunk. b. Water content of food. c. Formed by metabolism of food or of body if necessary.	— Excreted Water.	a. Visible Water Loss b. Insensible Water Loss. c. ? Water needed to build body tissue.

It will have been seen that the direct method of determining water exchange, although tedious and cumbersome, is essentially simple in principle. It has been extensively used in many investigations of the water exchanges of normal subjects and also of sick patients and yielded information of the greatest impottance. It is the method of choice at the present time.

* * * * * * * * * * *

Indirect Methods of Determining Water Exchange.

The principles involved in the determination of water exchange by indirect methods have been very ably discussed by P.H.Lavietes (37) and the succeeding discussion is very largely an outline of the principles he propounds.

The indirect approach to the study of water exchange is based upon the study of electrolyte metabolism. It has the advantage that it gives information, not only of the exchanges of fluids between the body and its environment but also concerning the distribution of fluids within the body.

Principles Involved.

I. It has been shown by Gamble and his Associates (38) that if fluids are lost by the body, then water and base (excluding calcium) are each lost in approximately the same proportions in which they exist in the plasma.It should therefore be possible from determined balances of cations to estimate water exchange. Such a procedure presupposes that total base is distributed evenly throughout the entire volume of the body fluids, and that the concentration of total base in these fluids remains constant while the volume of these fluids changes. This need not be true of individual cations. Recently more accurate determinations of serum base have shown variation of one to two per cent, and in unusual conditions much wider variations occur. But comparisons of tissues, transudates, and red blood cells have shown that the concentration of total base per unit volume of water are approximately alike in all these media. Thus in spite of minor variations from individual to individual there is considerable evidence that a change in the concentration of base in any portion of the body elicits changes in like direction and degree in all other portions.

2. Changes produced in the distribution of water between the cells and extracellular fluids of whole blood by the addition of (a) water. (b) solutes capable of traversing cell membranes and (c) solutes incapable of traversing cell membranes.

a. Klinghoffer (39) showed that when water was added to human blood in vitro, the added water is redistributed almost immediately in such a manner that cell and serum water are increased nearly proportionately. Since it has been shown previously that under these conditions no base traverses the cell membrane, the inference that the concentration of the base of cellular water falls nearly in direct proportion to that of the serum seems warranted.(40,41).

b. When urea or glucose solutions were added to blood, the water of the cells and serum increased nearly proportionately, the added solutes distributing themselves evenly thoughout all the water present (both intracellular and extracellular) without any exchange of base between cells and serum.

c. When hypertonic solutions of sucrise were added to blood, on the contrary water was withdrawn from the cells and the concentration of base in the water of the cells rose above that in the water of the serum.

These findings are in accord with the theory of osmotic pressure which demands that only those solutes to which the cell membrane is impermeable exert an osmotic influence upon the distribution of water between cells and serum. In the body, the total electrolyte concentration of the inorganic bases which are apparently unable to pass through cellular membranes and make up the major portion of the osmotically effective substances of the fluid media. Changes in the concentration of base in any portion of the body water should, then, be compensated for by like changes in the other portions if osmotic equilibrium is to be maintained. This has been found to be substantially true, and, although there is no direct evidence that the concentration of base in the water of tissues other than red blood cells varies directly with that of the serum, from theoretical considerations one would expect this to be true if the isotonicity of the body fluids is to be maintained, unless non-electrolytes, to which the cell membrane is not permeable, are quantitatively significant, or unless there is a change of pH and hence of base bound by protein.

If it is true that changes in the concentration of base are distributed over a large volume of fluid, even slight changes in concentration may be quite significant in attempts to telate balances of water and base. For example in a subject weighing 50 Kg. of which about 35 Kg. is water a change of two milliequivalents in the concentration of base would allow the gain or loss of 35 X 2 = 70 milliequivalents of base without a change in the volume of fluid in the body. conversely a change of 2 milliequivalents, in the concentration of base if this were originally 150 milliequivalents per liter, wuold be produced by a change in the volume of body fluids of $35 \times \frac{2}{150} = 0.467$ liters without either gainor loss of base by the body.

Total Water Exchange.

If base does tend to distribute itself throughout the fluid media of the body in definite and relatively constant proportions to water, it should be possible to estimate body water exchange from the balances and changes of concentration of base in serum by the following formula:

$$W_I B_I + b = W_2 B_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad \text{I.}$$

In which W_I and W_2 represent the volumes of water in the body at the start and at the conclusion of the period of study respectively; B_I and B_2 are the corresponding concentrations of Na + K in the water of the serum*; and b, the net gain or loss of Na + K by the body. The equation may be written:

$$W_I B_I + b = W_2 (W_I - \Delta W)$$

in which $\Delta W = W_2 - W_I$, or water exchange.

Solved for ΔW this becomes,

$$\Delta W = \frac{b + W_I \Delta B}{B_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 2.$$

in which $\Delta B = B_I - B_2$, the change of the concentration of base in the water of the serum. If the concentration of base does not change, the equation is simplified to:

$$\Delta W = \frac{b}{B} \quad \dots\dots\dots\dots\dots\dots \quad 3.$$

which represents essentially Gamble's method of calculation.

Equation 2 can be solved for total water exchange providing a value for the initial volume of fluid W_I can be found. This value may be taken as 70% of the initial body weight, with the understanding that this is merely an approximation.

* Na + K has been used rather than total base because the other bases, calcium and magnesium, are found in the water of the body in relatively small amounts and exert an osmotic effect that is small compared with their acid combining power because they are bi-valent and partly in undissociated combinations with protein. This is certainly true of serum, transudates, and red blood cells. Tissue cells however contain a considerable amount of magnesium, neglect of which may conceivably introduce error into calculations.

Changes in Volume of Extracellular Fluids.

Almost all the sodium of the body is confined to the extracellular fluids, and the same is true of chlorides if red blood corpuscles are excluded from consideration.(40). If this is true, extracellular water exchange (ΔE) may be calculated from sodium metabolism as follows:

$$Na_I\, E_I + b_{Na} = Na_2\, E_2$$

where Na_I and Na_2 represent the average concentrations of Na in extracellular water at the beginning and at the end of the period of study; E_I and E_2 represent the volume of extracellular fluids at corresponding times; and b_{Na} represents the Na balance. By substituting $E_I + \Delta E$ for E_2 in the above equation it may be solved for ΔE:

$$\Delta E = \frac{b_{Na} + E_I(\Delta Na)}{Na_2} \quad \dots\dots\dots\dots\dots\dots \quad 4.$$

Likewise if the Cl in the red blood cells is neglected (the red blood cells of a 50 Kg. man contain only about 75 milliequivalents of Cl, an insignificant amount in comparison with the Cl of the interstitial fluids.)

$$\Delta E = \frac{b_{Cl} + E_I(\Delta Cl)}{Cl_2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 5.$$

Theoretically if 4 and 5 are both accurate expressions of extracellular water exchange, it should be possible by equating the two, to solve for the initial volume of these fluids. Practically this is not possible because errors within the limits of analytical accuracy may prove of overwhelming significance.

The discussion of the indirect methods of determining water exchange has emphasised certain important principles. Practically Lavietes (37) has demonstrated their applicability. As yet however, for clinical purposes, the direct gravimetric method of estimating water exchange remains the method of choice. When analytical methods have been perfected, the indirect method outlined abovewill be the more valuable because it gives information, not only of the total water exchange, but also concerning the distribution of fluids within the body, derangements of which can so seriously affect body economy.

CHAPTER 3.

WATER BALANCE IN RELATION TO SURGERY.

It is only during the last seven years that the principles which have been outlined above have been applied to the practise of surgery. The old practise of starving and purging patients before operations was given up by progressive surgeons because it was gradually realised, from clinical experience, that such procedures far from helping a critically ill patient, actually jeopardised his life and made him less able to survive a major operative procedure. Surgery owes an incalculable debt to W.G.Maddock and F.A.Coller for their investigations into the water requirements of surgical patients. By applying the principles outlined by Newburgh and his associates, they have not only reduced the mortality of major surgical operations, but also the morbidity associated with such procedures. By determining the actual water requirements of such patients, they have placed fluid therapy in relation to surgery on an accurate quantitative basis thus obviating the harmful effects attendant upon dehydration and the risks which accompany the administration of excessive amounts of fluid. The succeeding discussion is based almost entirely upon the researches of Professor Maddock and owes such virtues as it may posses to his investigative genius. Maddock and Coller have repeatedly emphasised that in patients recovering from surgical operations unless an accurate record is kept, both of the intake and output of fluids dehydration is very prone to occur. This is especially true in cases who cannot, for a variety of reasons, ingest adequate amounts of fluid by mouth. In these circumstances it becomes incumbant on the surgeon to administer the necessary fluids by some other route, intravenously, per rectum etc. By following the procedures they have outlined, I showed, in a series of ten cases operated upon in the wards of The Royal Infirmary, Edinburgh, and treated by the usual post-operative routine regime of that Hospital, that dehydration occurred in every case. Eight cases carried to the third post-operative day were dehydrated on an average by 1852 cc. the maximum being 3565 cc. and the minimum 800 cc. The average dehydration of the ten cases at the end of the second post-operative day was I454 cc. Every case showed clinical signs and symptoms of dehydration, and the severity of such clinical phenomena varied also directly with the degree of their dehydration. That is there was, oliguria or anuria, rise in the blood non-protein nitrogen concentration indicating retention of urinary waste products, thirst, a parched dry tongue, and elevation of temperature which could not otherwise be explained. Maddock has shown that a rise in blood non-protein nitrogen does not usually occur as the result of dehydration until approximately 6% of the body weight has been lost in the form of water.(4I). If the water content of the body is 63% of the total body weight then dehydration becomes severe,as measured by a rise in blood non-protein nitrogen, when nearly IO% of the body water has been lost. It follows therefore that the majority of the cases investigated by me in The Royal Infirmary approached or exceeded this serious degree of dehydration.

It becomes necessary therefore to review the fluid losses which occur in surgical patients before, during, and after operations. These are:

I. Fluid deprivation before operation.
2. Fluid losses before operation which result from the disease itself.
3. Loss of blood during operation.
4. Loss of water during operation and in the immediate post-operative period from excessive perspiration, and evaporation from exposed tissues.
5. Losses which occur from vomiting, from the drainage of wounds etc. in the post-operative period.

I. Fluid Deprivation before Operation.

Once a routine preoperative measure, it has now been almost entirely given up. In some cases, however, such as obstructing gastric carcinomata, stenosing duodenal ulcer etc. the very nature of the disease precludes the adequate ingestion and absorbtion of water. Such cases require that their water needs shall be fulfilled by some other method of administration. In the absence of unusual water losses from vomiting, high fever etc., 2500 to 3500 cc. are required daily by adult patients, and this volume must be given if the patient is to be brought to operation properly hydrated.

2. Fluid Losses before Operation which result from the Disease itself.

Many examples of diseases which are accompanied by excessive loss of fluid may be given. For instance, high intestinal obstruction, and many other acute abdominal emergencies are accompanied by vomiting as the result of which the body water, in addition to its electrolytes, is depleted. Other disease which also are accompanied by great losses of water and electrolytes are the uraemia accompanying prostatic obstruction, acute middle ear disease accompanied by vomiting especially in children, intussusception, acute osteomyelitis accompanied by vomiting and high fever etc. Indded such examples may be multiplied almost indefinitely. It follws that many patients come under the care of the surgeon in a grossly dehydrated condition and will present, in addition to the symptoms and signs of their particular disease, the symptoms and signs of dehydration. Indeed it can be said with truth that the clinical picture of many diseases is that of dehydration with only additional details of history or sign or symptom. If the patient be weak and thirsty, has a dirty dry tongue, foetid odour to his breath, an elevated temperature, a weak but not necessarily rapid pulse, appears shrunken so that his skin envelops him in a loose inelastic bag, has sunken lustreless eyes and hollow temples; if he has passed no urine or it is scanty, concentrated, and contains little or no chlorides; if, in addition, his blood shows an increase in the concentration of non-protein nitrogen, a rise in the concentration of the plasma proteins, a rise in the red blood cell count and the haemoglobin concentration, and a decrease in the concentration of chlorine in the plasma, then the patient presents the fully developed picture of dehydration. It may not be possible to obtain all the information detailed above; the important clinical phenomena of dehydration are the appearance of the patient, the dry tongue and thirst, and the oliguria or anuria. Such patients have lost at least 6% of their body weight in fluids alone, and before any surgical procedures should be contemplated this amount of fluid lost must be replaced.

For example a 70 Kg. man whose body fluids have been depleted by 6% of his body weight, and who consequently presents the clinical picture of dehydration, will require at least 4200 cc. (7 pints) of fluid to make good the volume lost. The nature of the fluid to be given will be discussed later in this paper. This volume of fluid, 4200 cc. will only replace the fluid lost as the result of his condition; he will therefore require in addition fluid for his daily needs. For example if he requires 4200 cc.of fluid to replace that which he has lost he will need in addition a further 2500 to 3500 cc. to provide fluid for purposes of excretion etc. or on the day of admission a total vlume of approximately 7000 cc. (II½ pints.) This volume of fluid seems enormous, but if fluid therapy is to be conducted on rational lines such volumes must be given. An example of a case in which very large volumes of fluid were required may emphasise this point. In a patient with a duodenal fistula it was found necessary to administer intravenously daily for several days more than I0,000 cc. of fluid.

3. Loss of Blood during Operations.

Blood losses during operations are greater than is generally realised. Maddock and Coller (42) determined the blood losses in eleven patients undergoing a variety of procedures and their results are summarised in Table 8 which is copied from their paper.

TABLE 8.

Operation.	Volume of Blood Lost.
I. Partial gastric resection.	274 cc.
2. Excission of thyroglossal cyst.	I74 cc.
3. Repair of Inguinal hernia.	I47 cc.
4. Repair of Inguinal hernia.	54 cc.
5. Haemorrhoidectomy.	8 cc.
6. Appendectomy.	I4 cc.
7. Excission of retro-peritoneal teratoma.	546 cc.
8. Right radical mastectomy.	I272 cc.
9. Subtotal thyroidectomy.	I42 cc.
I0.Subtotal thyroidectomy.	36I cc.
II.Repair of ventral hernia.	306 cc.

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It will be seen that these losses of blood are considerable. In the case of the radical mastectomy 42 ounces of blood were lost and 4 to I0 ounces seems a usual amount of blood to be lost during a major surgical procedure. In general, they state, that the blood losses are greater when large areas are exposed and there is more or less continous oozing of blood than with haemorrhage from spurting vessels. Such blood losses cannot but contribute very considerably to shock and dehydration, and it follws that the surgical axiom of arresting haemorrhage immediately should be strictly adhered to.

4. Loss of Water during Operations, and in the Immediate Post-Operative Period, from Sweating and Evapdration from Exposed Tissues.

The volume of water lost from the skin and lungs during operation and in the immediate post-operative period, may be very considerable. In an investigation into this problem Maddock and Coller (43) have shown that as much as 705 grs. of water may be lost through this channel during the operation alone. Such a large quantity is accompanied by considerable visible perspiration and in the process of its secretion large amounts of sodium chloride also must be lost. Wiley and Newburgh (44) have demonstrated that for a normal subject under basal conditions, the insensible loss of water per square meter per hour is from I7 to 2I grs. During operation and in the recovery period, Maddock and Coller (44) showed that the insensible loss of water and visible sweating in grams per square meter per hour amounted to from eight to nine times that of normal subjects under basal conditions. This remarkable increase in the water loss from insensible perspitation and sweating is due to a number of causes. High temperature in the operating room (over 80 F.) definitely increases the loss of water through these channels because less heat can be dissipated by radiation. Excessive coverings expecially large mackintosh drapes, staining and moving under the anaesthetic, shock and inhalation or spinal anaesthetics also operate unfavourably. There is as yet inadequate information upon the effect of individual anaesthetics, but in the series reported by Maddock and Coller (44) minimal losses of water from insensible perspiration and sweating were observed when some basal anaesthetic, such as avertin was used in conjunction only with nitrous oxide and oxygen. In the absence of such basal anaesthetic in cases in which ether was required to effect an adequate depth of anaesthesia greatly increased losses were observed. During the recovery period of four hours Maddock and Coller (44) showed that water losses can be markedly decreased by reducing the coverings of the bed. The old fashioned"Ether" bed should therefore be abandoned and patients returning from the operating room should be placed in a normal bed with only one or two blankets. Lighted "shock" cages and an excessive number of hot bottles should also be discarded.

The loss of water from large exposed surfaces such as are seen during the operation of radical mastectomy may be considerable. There is no accurate information on this point as yet, but apart from the local damage to the tissues which accrues merely from exposure, it is logical that such areas, exposed frequently to light must loose water, and should therefore be covered as far as possible by warm packs soaked in normal saline.

5. Losses Which occur from Vomiting, from the Drainage of Wounds etc. in the Post-Operative Period.

These naturally vary from case to case. It is obvious however that such losses may be very considerable and must be taken into consideration when the daily volume of fluid to be administered is decided upon if water and electrolyte balance is to be maintained.

SUMMARY OF WATER BALANCE IN RELATION TO SURGERY.

. Before operations patients must be properly hydrated.

a. In elective operations in which the patient is not dehydrated from any cause the preoperative daily intake of fluid should be from 2500 to 3500 cc. no fluid being given by mouth during the three hours immediately preceding operation.

b. If the patient has been dehydrated, as for instance by vomiting, the fluid lost must be made good by the administration of a volume of fluid at least equal to 6% of the body weight.

. The anaesthetic used should be a combination of some basal anaesthetic such as avertin or paraldehyde, with nitrous oxide and oxygen. Because of the tendency to cyanosis which an adequate depth of anaesthesia with nitrous oxide and oxygen produces it is preferable to use cyclopropane or ethelene. Ether probably causes increased loss of water because of the peripheral vaso-dilation which accompanies its use. Whatever combination of anaesthetics be used the depth of anaesthesia should be sufficient to prevent moving and straining while under the anaesthetic.

3. The temperature of the operating room should be between 75 and 80 F. and should never exceed the latter figure.
4. The patient in the operating room should not be covered by more than one blanket or by mackintosh towels.
5. Every effort must be made to secure haemostasis immediately. Large raw oozing surfaces loose more blood than spurting vessels, which are rapidly clamped and such surfaces should be covered with towels soaked in saline and the bleeding controlled by pressure.
6. To prevent excessive losses of water from insensible perspiration and sweating, after operation the patient should be placed in a bed made up with a mattress spread, sheets and one or at most two blankets, in wards the temperature of which is about 65 F. Lighted shock cages and numerous hot bottles should be discarded, one or at the most two hot bottles at the patients feet being the ideal.
7. The output of all fluids must be accurately measured and charted. The volume of all vomitus, drainage fluid, diarrhoea etc. must be added to the volume of fluid which will be administered during the succeeding 24 hour period. Graphically the following chart explains such a calculation for the daily needs of surgical patients.

VOLUME OF FLUID LOST =VOLUME OF FLUID REQUIRED.

I. Insensible Perspiration, allow,		2000 cc.
2. Urine. The patient should excrete,		I500 cc.
3. Faeces, allow,		IOO cc.
4. Other losses, Vomitus,		x
Drainage,		x
Diarrhoel Stools,		x
	Total	3600 cc. + Other Losses.

Administer this volume of fluid by mouth or if this route is impracticable by intravenous infusion. During the 24 hours after operation an extra IOOO cc. of fluid should be given to compensate for the unusual losses during operation. The most valuable clinical index of hydration is the volume of urine excreted by the patient. If the volume of urine be less than 500 to 600 cc. and it is highly concentrated, then the patient is dehydrated and the blood non-protein nitrogen should be determined. If the concentration of the blood non-protein nitrogen is higher than it was pre-operatively then the patient is seriously dehydrated. If the patient be anuric, the hydration of the patient must be definitely established before any other measures are taken to promote the secretion of urine. Dehydration is by far the most common cause of oligutia or anuria.

By the application of these rules the surgical patient can be maintained in water balance, a state which will markedly lower both the mortality and morbidity of surgical procedures.

CHAPTER 4.

It now becomes necessary to discuss the methods by which fluids may be given and the solutions which may be administered.

Methods of Administration.

By Mouth.

This, the natural and one of the most efficient methods of administration, is to be preferred above all others. It has the merit of simplicity and is available even in a cottage in the Outer Hebrides. But, for a variety of reasons in the sick patient, especially the sick surgical patient, it may not be practicable. Some of these reasons are:

I. The administration of fluid by mouth may provoke nausia, vomiting, and even diarrhoea in patients recovering from operations which have required a general anaesthetic.

2. It may be desired to limit or even prohibit the intake of fluids by mouth, as for instance after operations on the stomach, severe haematemesis, etc. (Although the limitation of fluids by mouth after gastric operations has been generally practised for many years, there is a growing body of opinion which believes that small amounts of sterile water frequently administered are actually beneficial after such operations. The water cleanses and moistens the mucous membranes of the mouth, pharynx, and oesophagus and by gently washing away accumulated exudates from the neighbourhood of the suture lines favours rapid and sound healing. Such exudates must become infected and add to the complication of sepsis at the suture lines inevitable in operations which require intestinal anastomosis. One ounce of tepid sterile water every hour is like nectar to the patient who has undergone a gastric resection and is not sufficient to disturb the rest which is also essential for rapid healing. By the routine of continuous gastric drainage larger amounts of sterile water more frequently administered adds lavage to the cleansing effect of the water as well as removing swallowed air and undesirable gastric and duodenal secretions from the neighbourhood of the suture lines.)

3. Inability to Swallow. Dysphagia due to lesions of the upper alimentary tract, quinsy, diphtheria, stricture of the oesophagus, bulbar palsy etc. may prohibit the ingestion

of fluid by mouth. In pyloric stenosis, although fluids may be administered by mouth, absorbtion and therefore utilisation may be completely in abeyance. Therefore, until the obstruction has been overcome, it becomes imperative to administer the necessary fluids and electrolytes by some other route.

4. The very nature of the disease e.g., perforated peptic ulcer, intestinal obstruction etc, may prohibit the administrarion of fluids by the gastro-intestinal tract.
5. Functional or Reflex derangements of the gastro-intestinal tract such as are seen in the pernicious vomiting of pregnancy, the vomiting which accompanies increased intra-cranial pressure, in glaucoma, and in severe migraine may render the administration of fluids by mouth impossible.
6. Certain diseases characterised by gross upset of metabolism or toxic states may be associated with inability to ingest fluids by mouth for example uraemia, eclampsia gravidarum, and remote infections in children.
7. Inability to co-operate may be a bar to the to the ingestion of fluids by mouth. For example in coma, in delirium, in memingitis, head injuries, cerebral vascular lesions, diabetic coma, narcotic poisoning, insanity, in infants, and in great weakness.
8. In conditions such as haemorrhage, shock etc, which are characterised by marked reduction in circulating blood volume it is necessary to restore rapidly the circulating fluid volume. The intravenous administration of fluids effects this much more rapidly than the ingestion of fluids by mouth.
9. In conditions in which salt is urgently required by the body its administration by mouth may not be possible in large enough quantities without provoking nausia and vomiting.

From the rather heterogenious examples given above it is obvious that if fluids and electrolytes are necessary to the patient who cannot ingest them by mouth other methods of administration must be employed. These other methods are;

I. By the Rectum.

This method of administration is of considerable value but it depends for its success upon the strict observance of the principles of its technique enunciated by Murphy of Chigaco ( ). These are:

A. That the pressure within the rectum must not be appreciably raised.

B. The rate of administration must be uniform and never excessive.

These desiderata are effected by:

I. The height of the reservoir should never be more than I5 inches above the anus and preferably only 4 to 7 inches, thus reducing the risk of raising the intrarectal pressure hydrostatically.

2. There must be no constriction between the reservoir and the rectal nozzle such as a drop bottle which might be an obstacle to the passage of flatus along the tube. The tubing between the reservoir and nozzle must have an internal diameter of not less than one quarter of an inch and should be pressure tubing to prevent accidental constriction. The opening or openings in the nozzle must be large.

Both water and saline solutions may be administered by the rectum. If physiological salt solution be given the rate of absorbtion of both water and salt is slow. If distilled of tap water be given and the electrolyte content of the body is normal, considerable quantities of water, up to I4 pints a day may be absorbed but it has the disadvantage that electrolytes (mainly chlorides) diffuse from the body into the water in the colon. This is undesirable in patients with hypochloraemia, in which state also, owing to the lowered osmotic gradient between the blood in the bowel wall and the water in the colon, the rate of absorbtion from the colon is less rapid. It is also conceivable that certain toxic products of bacterial activity in the colon may be carried into the portal circulation with the water absorbed and thus throw an extra strain on a possibly already damaged liver.

Glucose administered per rectum probably is not absorbed by the colon, but, if there be regurgitation of the glucose solution through the ilio-caecal valve into the terminal ileum small quantities of glucose may become available to the body, Glucose may have the disadvantage, however, of provoking fermentation in the colon and causing the onset of diarrhoea. All other forms of nutrient enemata containing for instance eggs etc., are practically valueless and may even be harmful.

2. Hypodermoclysis or Subcutaneous Injection.

This method of administering fluids is of great use but has several drawbacks. The usual technique is to inject fluid under both mammary glands or into the subcutaneous tissues on the outer or inner aspects of both thighs. Absorbtion is certain and moderately rapid, but again is controlled by the same considerations of osmotic gradient which governed the absorbtion of fluid from the colon. Only sterile fluids, isotonic with the blood, should be given i.e., 0.9% sodium chloride solution, 5% glucose solution, Ringer's solution or I.8% sodium lactate solution, and an absolutely aseptic technique must be adopted. Hypotonic fluids, notably distilled water, may cause great pain at the site of injection, and, even when all precautions of sterility and asepsis are faithfully carried out, aseptic necrosis may ensue at the site of injection.The actual pain caused by such injections, even of isotonic solutions, may be in some measure minimised by the addition of 300 milligrams of novocain to each liter of fluid injected.

The realive ease, flexibility, safety, and general applicability of the untravenous administration of fluids has resulted in the decreasing use of hypodermoclysis as a mehtod of fluid administration.

3. Intraperitoneal Injection.

Various fluids have been injected into the peritoneal cavity especially of infants whose veins are small and whose tissues are not very suitable for hypodermoclysis. Physiological salt solution, 5% glucose solution, Ringer's solution, and even whole blood has been introduced into the peritoneal cavity and absorbtion from it may be rapid. The effects of such injections have been considered in the discussion on the results of the experiments of Darrow and Yannet (27), and in view of the many undesirable results of such injections this method of fluid administration should be discarded. It also carries with it the dangers of infection and of injuring the peritoneum and abdominal viscera. Intractible abdominal distension, peritoneal exudation and possibly the formation later of adhesions are also potential dangers. Blood certainly should never be injected into the peritoneal cavity.

, Venoclysis or Intravenous Infusion.

This theraputic measure is one of the most valuable in medicine. A great variety of fluids and drugs may safely be administered intravenously. By this method hypertonic solutions such as I0 to 50% glucose solution, 50% sucrose solution, 5% sodium bicarbonate solution, or hypotonic solutions, or acid or alkaline solutions may be given when needed. Again, sterility of the injected fluid and an aseptic technique are essential, and the rate of administration must be under control- a suitable speed of injection is from 300 to 500 cc. per hour. The actual technique of the intravenous administration of fluids deserves description.

Apparatus.

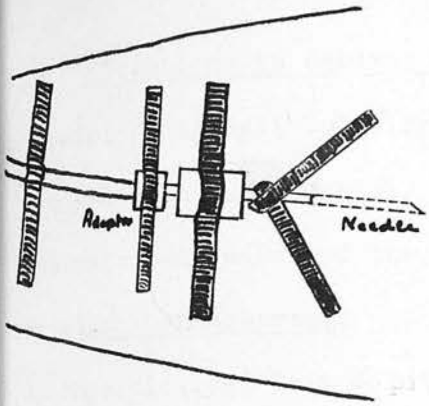
The fluid to be administered is placed in a sterile container of the Farquharson type suspended at a height of about four feet above the level of the patient from a standard which may be attached to the bed. This container is connected by a short length of rubber tubing to a dropper bottle. Approximately 2 drops per second from a normal sized dropper will give a rate of administration of about 500 cc. per hour, and regulation is effected by an adjustable screw clip placed on the rubber tubing connecting the fluid container to the dropper bottle. The dropper bottle is connected by further rubber tubing to a spherical glass air trap and this in turn to an adapter for carrying an intravenous needle. This needle should be an inch to an inch and a quarter long, and it should have a medium bevel to the point, about Gauge I8 to 20 Luer. Smaller needles reduce the possible rater of administration, larger needles are unnecessary and give rise to considerable pain when inserted. It is quite unnecessary to incorporate a method of warming the fluid during administration but special precautions are essential to ensure the cleanliness and sterility of the whole apparatus. Special rubber tubing for this purpose is now on the market and should be used.

A sterile Luer or Record syringe with suitable needle, tourniquet, sterile square, spirit swabs and quarter inch adhesive tape complete the necessary apparatus.

Technique.

The container, rubber tubing, and air trap are filled with the solution to be injected, and rate of flow adjusted to one drop in two or three seconds. A tourniquet is placed around the arm or leg to distend the superficial veins of the extremity selected; it should not be so tightly applied as to obliterate the pulse. The limb is then cleansed with spirit and suitably draped. In the leg a suitable vein is the great saphenous immediately anterior to the medial malleolus. In the arm, any vein, either on the back of the hand or on the forearm may be used, but it is to the advantage both of the surgeon and of the patient to select one of medium size, as the needle lies more snugly in a vein of approximately the same calibre as itself and thus there is less likelyhood of injuring the intima of such a vein and causing thrombosis. The site of the injection should also be distant from a flexure as the needle may perforate the vein if the joint is flexed causing stoppage in the administration and leakage into the tissues.

A suitable vein and favourable site having been selected, the needle is inserted into it in the usualway up to the hub. Blood is then withdrawn into the syringe to confirm the proper insertion of the needle and for any bio-chemical analyses which may be desired. The tourniquet is now released and the syringe disconnected from the needle with as little movement as possible to prevent injury to the vein. The adapter on the intravenous apparatus is now connected to the needle and the rate of flow of the solution through the dropper is increased to two to three drops per second. The needle is secured to the limb by passing a peice of quarter inch adhesive? tape around the hub and crossing the two ends on either side. Further security is afforded by placing lengths of adhesive tape across the rubber tubing between the needle and the air trap thus anchoring it to the limb, vide diagram overleaf.



If properly inserted a considerable range of movememt is possible for rhe limb without any risk of intefering with The smooth working of the apparatus or injuring the vein. By following this technique fluid may frequently be administered through the same needle for 24 to 36 hours. The complications of this method of administration are:

I. Perforation of the vein by the needle with consequent leakage into the surrounding tissues, if the needle is inserted near a flexure or the patient be restless.

2. Thrombosis of the vein from injury to the intima. This complication is more likely to occur when the rate of flow is slow.

3. Sepsis. This is liable to occur if the technique of insertion has been faulty in regard to asepsis or the apparatus has not been properly sterilised.

4. Violent reactions have occured from the administration of fluids intravenously. These include rigors and high temperature, and phenomena akin to allergy. Such reactions have been shown to be due to unclean, though possibly sterile apparatus, and can be almost completely obviated by the use of the special tubing and the strictest cleansing of all apparatus before sterilisation.

In twelve hours at a rate of administration of 450 cc. per hour 5400 cc. of fluid can be given. This volume is greater than the daily amount which, as a general rule, is needed by a patient during a 24 hour period. By confining the fluid administration to the day time the patient is allowed undisturbed sleep during the night. It also has the advantage that the work of the night staff in a busy ward is considerably reduced. By this techñique of inserting and withdrawing the needle daily different veins are used and there is thus less risk of sepsis than if a cannula is left in for a two or three day period.

Only in the very obese, or in very restless patients should it be necessary to tie in a cannula - an operation which inevitably leaves a scar. In infants, the jugular or scalp veins are usually available, but in an emergency the superior sagital sinus may be used by puncture of the anterior fontanelle.

Solutions in General Use.

I. Physiological Salt Solutions. There are many such solutions and, as a group, they are among the most useful. The following formulae are taken from the British Pharmacopoea Codex and the United States Pharmacopoea.

British Pharmacopoea.

A. Physiological Salt Solution.

A sterile aqueous solution containing sodium chloride 0.9% W/V.

B. Dextrose and Sodium Chloride Solution, or Glucose Saline Solution.

A sterile aqueous solution containing 5% W/V of dextrose and 0.9% W/V of sodium chloride.

C. Liquor Ringer B.P.C.

Sodium chloride	7.0 Gm.
Potassium chloride	0.I4 Gm.
Calcium chloride	0.I2 Gm.
Sodium bicarbonate	0.2 Gm.
Sterile distilled water to	I000.0 ml.

This solution is isotonic with frogs serum.

D. Liquor Ringer - Locke B.P.C.

Sodium chloride	9.0 Gm.
Potassium chloride	0.42 Gm.
Calcium chloride	0.24 Gm.
Dextrose	I.0 Gm.
Sodium bicarbonate	o.5 Gm.
Sterile distilled water to	I000.0 ml.

This solution is isotonic with the serum of mammalian blood.

E. Liquor Ringer - Tyrode B.P.C.

Sodium chloride	8.0 Gm.
Potassium chloride	0.2 Gm.
Calcium chloride	0.2 Gm.
Magnesium chloride	0.0I Gm.
Dextrose	I.0 Gm.
Sodium acid phosphate	0.05 Gm.
Sodium bicarbonate	I.0 Gm.
Sterile distilled water to	I000.0ml.

This solution is isotonic with the serum of mammalian blood.

United States Pharmacopoea.

F. Physiological sodium chloride solution U.S.P.

Sodium chloride	8.5 Gm.
Water freshly distilled a sufficient quantity to make	I000 c.c.

G. Locke - Ringer's Solution U.S.P.

Reagent sodium chloride	9 Gm.
Reagent potassium chloride	0.42 Gm.
Reagent calcium chloride	0.24 Gm.
Reagent magnesium chloride	0.005 Gm.
Sodium bicarbonate	0.5 Gm.
Dextrose	0.5 Gm.
Water, recently distilled from a hard glass flask, a sufficient quantity to make	1000 c.c.

In recent years the larger manufacturing chemists are providing physiological solutions of electrolytes in convenient containers. The formulae of such solutions vary from firm to firm. The formula of such a commercially produced solution is that of the Abbott Company's Ringer's solution.

Every 1000 c.c. of sterile solution contains:

Sodium chloride	7.0 Gm
Potassium chloride	0.3 Gm.
Calcium chloride	0.25 Gm.

In chemically pure water free from pyrogenic substances.

An examination of the formulae of these various solutions discloses their variability. It must be stressed that for efficient and accurate administration of chlorides only solutions of known and unvarying composition should be used. Although Ringer - Locke's solution has certain theoretical advantages in that it contains, in addition to sodium chloride, other salts normally present in mammalian blood, for practical purposes the therapeutics of sodium chloride is overwhelmingly more important than that of the other salts in the majority of patients. And, as the figure 0.9% sodium chloride of the B.P.C. solution is more convenient for purposes of calculation than that of 0.85% of the U.S.P., the physiological sodium chloride solution of the British Pharmacopoea should be used.

Physiological salt solution is isotonic and neutral in reaction and may be given by any of the methods of administration already discussed.

2. Glucose Solutions.

Five per cent glucose solution is isotonic and may be given by venoclysis or by hyperdermoclysis. Stronger solutions of glucose have been frequently used, 10%, 20%, or even 50%. These must be given only by venoclysis as they are highly irritating to the tissues, and, even if given intravenously, such hypertonic solutions frequently cause thrombosis of the vein especially if the vein has been injured by the insertion of the needle. I consider that the 20% and 50% solutions of glucose are only indicated in the hypoglycaemia which accompanies an overdose of insulin. Under the unusual circumstances of partial starvation which generally exists after operation for a number of days, the metabolism of the injected glucose is incompletely understood. Normally most of it would be absorbed by the liver and muscles and transformed into glycogen, thereafter probably to be reconverted into glucose and, by incompletely understood intermediate stages metabolised to carbon dioxide and water. Each gram of glucose on oxidation provides 4 calories for the body's energy requirements and 0.6 grams of water. Thus, a liter of 5% glucose solution will give 200 calories and 30 grams of water which adds to the hydration of the subject. S.B.Winslow, in a recent as yet unpublished investigation has ably emphasised the curious paradoxical phenomenon of absorbtion and utilisation of glucose solutions. He found that in patients who were given 5% glucose solution at approximately 500 c.c. per hour up to their water requirements, approximately 80% developed glycosuria in which an average of 2% of the injected glucose was lost in the urine. That is, if 3000 c.c. of 5% glucose solution had been injected, of the 150 grams of glucose so given, 3grams were lost. In patients given 10% glucose solution at the same rate up to their water requirements, 100% developed glycosuria in which an average of 6% of the injected glucose was lost in the urine. That is, if 3000 c.c. of 10% glucose solution had been injected, of the 300 grams of glucose so given, 36 grams were lost. Thus, in 80% of administrations of 5% glucose solution 147 grams of glucose were retained and 3 grams were lost; and, in the 10% glucose solution administrations, 264 grams were retained and 36 grams were lost. In the present state of our knowledge it is my opinion that the advantage of the extra retention and presumably utilisation of glucose (264 grams to 147 grams) when 10% solutions are given is more than offset by the disadvantages of dehydration which may result from the increased excretion of urine necessary to excrete 36 grams of glucose. Therefore the isotonic 5% solution of glucose should be used for intravenous administration in all surgical cases.

The other solutions of glucose include combinations of glucose with sodium chloride or with gum acacia. In my opinion these solutions have no advantage peculiar to themselves which cannot be gained by the administration of solutions of these varios substances separately.

3. Sucrose Solution 50%.

This strongly hypertonic non-toxic solution may be given in order to lower intracranial pressure. Sucrose thus given is quantitatively excreted in the urine and has a strongly diuretic effect. It posseses the great advantage over 50% glucose solution of not diffusing into the cerebrospinal fluid as does glucose which thus produces a secondary rise in cerebrospinal fluid later.

4. Sodium Bicarbonate Solution 5%.

In severe acidosis, as for example in diabetic acidosis and the acidosis accompanying the diarrhoea of infants, it may be advisable to give an alkaline solution intravenously in addition to water and sodium chloride to make good the accompanying dehydration and frequent hypochloraemia which occur in these diseases. 5% sodium bicarbonate solution is hypertonic and therefore must be given intravenously. It also has the disadvantage that it requires to be sterilised by a special technique because, when heated, sodium bicarbonate loses CO_2 and becomes changed into the very alkaline and toxic sodium carbonate. Therefore, since a suitable alkaline solution in sodium lactate solution I.8% is available, the administration of sodium bicarbonate solution should be discontinued.

5. Sodium Lactate I.8%.

This fluid is isotonic and neutral in reaction and may be administered either intravenously or interstitially. In the body, its lactate radicle is gradually converted to glucose thus liberating sodium and conferring on the solution its alkaline property. This fluid therefore has real merit in the treatment of acidosis when used with discretion. The administration of excessive amounts may give rise to oedema owing to the liberation of sodium and thus consideration must guide and limit the volume of the solution given.

6. Acacia Solution.

This solution, consisting of 6% gum arabic made up in 0.9% sodium chloride solution in both the British and United States Pharmacopoeae was extensively used during the Great War in conditions of acutely reduced blood volume such as result from shock and haemorrhage. It is a colloidal solution which leaves the blood stream very slowly, and by virtue also of the colloidal osmotic pressure exerted tends to draw fluids from the interstitial spaces into the blood. It should be administered slowly, not more than 20 cc. per minute. It may cause hepatic damage and repeated injection may give considerable reactions of an anaphylactid character. It may therefore be said that, in conditions of acutely reduced blood volume such as shock and haemorrhage, gum acacia solution should be used only if blood transfusion cannot for any reason of time or circumstance be carried out; and that, repeated injections of gum acacia solution should never be given, especially if there is a considerable interval between such injections.

7. Blood.

Blood transfusion is so important a procedure and of such great therapeutic value that it can be classed as a life saving measure of the first magnitude. It is not the aim of this paper to discuss blood transfusion in technical detail but the general indications for its adoption are:

I. To restore blood volume.

2. To provide some substance needed by the patient which is contained in blood.

a. Haemoglobin - for acute or chronic anaemia.

b. Serum proteins.

c. Electrolytes - blood serum contains these substances in ideal concentrations, and it is probable that this fluid may be extensively used in the future.

d. White blood cells. The blood of patients with myelogenous leukaemia has been used sucessfully for the emergency treatment of agranulocytosis.

e. Antibodies - Convalescent serum of saes who have had measles for the treatment of the early stages of the disease or of contacts. Several other diseases have been treated in this way, e.g. poliomyelitis.

f. Substances necessary for the normal coagulation of the blood, e.g. for the treatment of haemorrhage in a haemophilic.

3. To act as a general tonic in marasmic cases and in severe infections. This group is indefinite and the effects of bolld transfusion may be dramatic or completely without success.

Blood may be given in a single transfusion of 400 to 600 cc. or by continuous drip transfusion over several days during which 6000 to I0000 cc. of blood or even more may be administered but, however administered, the necessary conditions of sterility and compatibility must be observed.

To summarise the above, normal saline solution, 5% glucose solution, I.8% sodium lactate solution and blood itself are each invaluable when their use is indicated. Properly used each may be life saving, but when improperly used each solution may be actually dangerous.

CHAPTER 5.

THE METABOLISM OF CERTAIN BODY ELECTROLYTES.

The water of the body has been divided into two fractions. The first exists inside the body cells and acts as the solvent for intracellular substances and is called the intracellular water. The second exists in the extracellular spaces, acts as the solvent for substances in the extracellular spaces of the body and is called the extracellular water. In the adult human being the distribution of water between the cells and the extracellular space is approximately as follows.

A. Intracellular Water. Forty per cent of the body weight, or sixty three and a half per cent of the total body water.

B. Extracellular Water. Twenty three per cent of the body weight, or thirty six and a half per cent of the total body water.

In other words the volume of water contained in all the body cells is approximately 1.74 times the volume of the water which exists in the extracellular spaces. In both these fractions of the body water there are substances in solution which exert an osmotic pressure, i.e., there are solutes in both compartments to which the cell membrane is impermeable as only such substances are capable of exerting an osmotic influence. As the total osmotic pressure of the serum and other extracellular fluids and that of the fluids in the cells is the same, it follows that alterations of osmotic pressure in one compartment, the result either of changes in the water content of that compartment or in the amount of its osmotically effective substances, will cause the passage of water into or out of the other compartment until the osmotic pressure on both sides of the cell membrane is again equal. The values given above for the volumes of the intracellular and extracellular water must therefore be only approximate and inconstant, because, during life, the concentration of osmotically effective substances in the extracellular fluids especially is constantly changing as the result of the ingestion or excretion of such substances or of water itself.

The total osmotic pressure of the body fluids is about 8 atmospheres (45) and is due to:

A. Non-Electrolytes.

These contribute only a small quota to the total osmotic pressure and are equally distributed between the intracellular and extracellular fluids. They merely raise the general level of the osmotic pressure of the body and do not affect water distribution between the cells and the extracellular spaces.

B. Electrolytes.

I. Organic Ions. These contribute so little to the osmotic pressure of the extracellular fluids that, in these fluids, they may be nearly neglected as factors in the distribution of water between the cells and the extracellular spaces. They are, however, of great importance as factors in the distribution of water between subdivisions of the great extracellular space, for instance between the water of the plasma and that of the interstitial fluid. The organic ions very largely responsible for the distribution of water between the plasma and the interstitial fluid are serum albumen and serum globulin. The ions together exert an osmotic pressure of about 30 mm. of mercury which continually attracts water from the interstitial space against the capillary blood pressure which tends to force fluid out from the capillaries into the interstitial spaces. If the concentration of the serum proteins is reduced, as for example it is in malnutritional oedema and parenchymatous nephritis, then the interstitial fluid will increase at the expense of the blood plasma and generalised oedema will result. From the surgical point of view this possible reduction in protein osmotic pressure may be of importance in the production of oedema during the administration of fluids, especially saline solutions, intravenously.

In blood cells about one third of the base is made up of protein or other colloidal anions, and presumably the tissue cells resemble the blood cells in this respect. It follows therefore, that in contra-distinction to the minimal effects which organic ions in extracellular fluids exert on the distribution of water between the extracellular and intracellular spaces, the intracellular organic ions must considerably influence the partition of water between the two spaces.

2. Inorganic Ions - Basic and Acidic.

The basic ions of the extracellular and intracellular fluids are not interchangeable because the cell membranes are almost impervious to them. Therefore their concentrations control the electrolyte osmotic pressure of their respective fluids and hence the distribution of water between the cells and extracellular fluids. The important basic ions are sodium and potassium, all the common salts of which are freely soluble. This property of solubility normally ensures complete absorbtion from the intestines, but it also carries with it the disability that the body is unable to store reserves of these elements in an insoluble and inactive form. In spite of their similarity chemically and physically, they fulfil quite different biological roles.

Sodium forms 94% of the total base of all extracellular fluids with two exceptions:

a. The gastric juice, in which hydrogen forms 60 to 70% of the total base.

b. The semen, in which potassium forms 17% of the total base instead of the usual 3%, to the partial displacement of sodium as the predominant extracellular base in this fluid.

Potassium forms the predominant base in the cells. Its replacement by rubidium has been found possible in certain diatoms, and uranium has been found to be a satisfactory substitute for potassium in fluids used in perfusion experiments to maintain the frogs heart beat. Although potassium replacement has not been fully explored experimentally, it can be stated that potassium is both essential to life and forms the predominant base inside the cells themselves.

The Acidic Ions in the body fluids which have impottant effects on the distribution of water are chlorine, bicarbonates, and phosphates both organic and inorganic. Others of much less importance are the various organis acidic ions. The metabolism of chlorine will be discussed fully,but, because this paper has no new information to add concerning the other acidic ions they will not be discussed in any detail.

The Metabolism of Chlorine.

The following discussion of some of the theoretical aspects of chlorine metabolism is derived very largely from the very clear account of the subject in Quantitative Clinical Chemistry : Interpretations. J.P.Peters and D.Van Slyke.

Chlorides have been found in all the tissues of the organism almost entirely in the form of inorganic compounds. Because the pH of the tissues is to the alkaline side of the isoelectric points of the proteins, the inorganic chlorides presumably exist, not as protein chlorides, but entirely in the form of neutral salts of the alkali metals. As the base of the cells is chiefly composed of potassium and that of the extracellular fluids of sodium, it follows that potassium chloride predominates in the cells and sodium chloride in the extracellular fluids.

The Distribution of Chlorides between the Cells and Body Fluids.

Donnan Equilibrium.

Since chlorides have been found in all the cells and fluids of the body, it has been inferred that cell boundaries are in general pervious to the chloride ion. In lymph and serous fluids the chlorine concentration is a few per cent higher than in blood plasma. In the red blood cells it is only about half as high and in muscles less than one third as high as in the plasma. The chief causes of the inequality of distribution of chlorine and bicarbonate between plasma and blood cells have been found to be:

1. In the cells an important part (up to nearly half) of the base, potassium, is in the form of haemoglobin salts, leaving only the balance to combine with chlorine and bicarbonate. In the plasma, on the other hand, only about one tenth of the base, sodium, is combined with protein thus leaving nine tenths to combine with chlorine and bicarbonate.

2. The lower water content of the cells (65 to 85%) as compared with the plasma (92%) diminishes the total electrolyte concentration per cubic centimeter of cells as compared with that per cubic centimeter of plasma, since per gram of water the total concentration of osmotically active electrolytes is equal in cells and plasma.

In tissues other than red blood cellsthe alkali binding powers of the proteins are still unknown, but the variable chloride concentrations encountered in these tissues are probably determined by the same factors discussed above.

The varying CO_2 of the blood alters the distribution of the chlorine as well as of bicarbonate between the cells and plasma. If the CO_2 tension is raised more H_2CO_3 is formed. This combines with part of the base, potassium, previously bound by haemoglobin forming $KHCO_3$ in place of potassium haemoglobinate. The equilibrium of the reaction

$$K_2CO_3 + K_2(Hb) \rightleftharpoons KHCO_3 + KH(Hb)$$

is shifted from left to right; (the formulation of potassium haemoglobinate as $K_2(Hb)$ is an approximate expression of the fact that, at the pH of normal blood, I mol. of haemoglobin is combined with about two equivalents of Potassium).

According to Donnan's law (46) the distribution of the diffusible monovalent anions, Cl' and HCO_3', should be equal where the system is at equilibrium, so that in concentration terms

$$(HCO_3')_{cells} : (HCO_3')_{plasma} = (Cl')_{cells} : (Cl')_{plasma}.$$

The formation of additional HCO_3 in the cells has unbalanced this equilibrium. In order to restore it HCO_3 diffuses out of the cells into the plasma, while an equivalent of Cl diffuses into the cells from the plasma until the cell: plasma ratio of the active concentrations of Cl' and HCO_3' anions are restored to equality. As the result of these reactions bicarbonate of both cells and plasma is increased, the cells gain some chloride from the plasma and Cl' and also the HCO_3' concentrations in the two phases become more nearly equal. Furthermore, to transfer HCO_3' from cells to plasma, by increasing the $NaHCO_3$ of the latter, serves to diminish the acidifying effect of the H_2CO_3.

The distribution of the blood water between the cells and plasma is also altered by the reactions that follow increase in the CO_2 tension. The increase in Cl' and HCO_3' anions in the cells causes an increased osmotic attraction for water, and in consequence water passes from the plasma into the cells and tje latter swell.

The effect of the above reaction on the acid base balance of the blood is to enable the cells buffers (chiefly potassium haemoglobinate) to share their stabilising buffer effect with the plasma. The plasma bicarbonate is increased by means of HCO_3' anions which were formed in the cells by the reaction of H_2CO_3 with $K_2(Hb)$ and then exchanged for plasma Cl'. Increase in bicarbonate decreases the hydrogen ion concentration according to the familiar Henderson equation:

$$H^+ = K' \frac{H_2CO_3}{BHCO_3}$$

The effect of increase in H_2CO_3 in raising the H is therefore in part neutralized by the simultaneous increase in $BHCO_3$. The bicarbonate increase in the plasma is due indirectly to the chlorides, because the bicarbonate anions could not have been transferred from the cells to the plasma if the latter had had no Cl' anions to exchange for them. The chlorides, by making such exchanges possible, play an important part in the interchanges of buffer effects between the richly buffered cells and the poorly buffered plasma.

There is increasing evidence that the chlorides assist in a similar interchange between the tissue cells and the intercellular fluids of the body in general which stabilises the acid/ base balance of the fluids. To summarise the above discussion.

1. With the system in equilibrium the following conditions exist:

a. In both cells and serum the positive and negative ions balance.

b. The ratios

$$\frac{(Cl')c}{(Cl')s} \quad \text{and} \quad \frac{(HCO_3')c}{(HCO_3')s}$$

are equal and in conformity with Donnan's law.

c. The osmolar concentrations obtained by adding $(B^+) + (Cl') + (HCO_3')$ are equal in the serum and cells respectively.

2. If the CO_2 tension be now increased:

a. The pH of the system is lowered.

b. Some of the base formerly bound by haemoglobin as B.Hb shifts to $BHCO_3$, HCO_3' replacing Hb'.

This results in a greatly increased concentration of HCO_3' in the cells and obviously makes

$$\frac{(HCO_3')c}{(HCO_3')s} > \frac{(Cl')c}{(Cl')s}$$

which is contrary to Donnan' law. The HCO_3' in the cells also causes the osmolar concentration there to exceed that in the serum. The system is therefore not in equilibrium and Cl' migrates from the serum to the cells and HCO_3' from the cells to the serum until again

$$\frac{(HCO_3')c}{(HCO_3')s} = \frac{(Cl')c}{(Cl')s}$$

To restore osmotic equilibrium water also migrates from the serum into the cells until the osmolar concentrations in both are equal. The impermeability of the cell membrane to cations prevents the diffusion of BCl and $BHCO_3$ from cells to serum to assist in the restoration of osmolar equality which must therefore be accomplished by the transference of water.

The system is now in equilibrium again.

According to Donnan's law the distribution ratio at equilibrium of the active concentrations of two diffusible monovalent anions, such as Cl' and HCO_3', between two solutions separated by a membrane permeable to both, must be the same. If the degrees of dissociation of chloride and bicarbonate into ions in the plasma and cells were equal, and likewise the activity coefficients of the dissociated ions, these simple molal concentrations ratios wuold, in accordance with Donnan's law be equal. If the dissociation and activity coefficients were not the same throughout, the two ratios wuold differ, one being F times as great as the other.

$$\frac{(HCO_3')\text{cells}}{(HCO_3')\text{plasma}} = F\,\frac{(Cl')\text{cells}}{(Cl')\text{plasma}}.$$

where the brakketed values indicate molal concentrations of bicarbonate and chloride.

Under conditions of pH7.4 and complete oxidation, in human subjects the F factor has been found to be from 0.80 to 0.90 and it remains practically constant under the influence of changing O2 and CO2 tensions. That is, the chloride inequality between the cells and plasma is IO to 20% greater than the bicarbonate inequality, although the two show parallel changes under varying influences. In both normal and pathological cases the HCO_3 per gram of cells was 53 to 58% of that per gram of serum, this would make the Cl content per cubic centimeter of cells 49 to 54% of that per cubic centimeter of serum. It has been estimated (47) that the percentage concentration of chlorine in the adult human body is 0.15% of the total body weight. Therefore, in a 70 Kg. individual there are 105 grs. of chlorine. Under ordinary circumstances normal human plasma contains from 352 to 383 mg. per 100 cc. or 99 to 108 milliequivalents of chlorine per liter. It has already been poimted out that the composition of plasma may be considered to be representative of the composition of other extracellular fluids, and that the extracellular fluids constitute approximately 23% of the total body weight. Therefore if the average chlorine concentration in extracellular fluids be taken to be 370 mg. per cent then the total chlorine present in the extracellular fluids of a 70 Kg. man is $\frac{70 \times 23}{100}$ x 370 mg.% or 59.6 grams, and that present in the intracellular fluids of the same individual is 45.4 grams. Therefore, since the intracellular fluids constitute approximately 40% of the total body weight, the concentration of chlorine in the intracellular fluids is approximately 162 mg. % or 45.6 milliequivalents per liter. Expressed in terms of sodium chloride the concentration of sodium chloride in the intracellular fluids wuold be 267 mg.% which is in reasonably close agreement with the value for the sodium chloride concentration of red blood cells which have been found to contain 2.90 grams per liter of cells.(48) There is however a growing belief that the tissue cells themselves contain only minimal quantities of chlorine and that the values obtained (mammary gland 4.09; lungs 4.07; kidneys 3.75; salivary glands 3.06; spleen 2.55; heart 1.70; liver 1.48; muscle 0.05 to 0.13 grams per Kg.) (48, 28), are largely dependent on the vascularity of the tissue and the amount of blood and lymph which it contains, and are never equal to the concentrations found in these fluids. At the present time it is impossible to give a final opinion on the is important matter. The diagram overleaf depicts the composition of certain body fluids and secretions in milliequivalents per liter.

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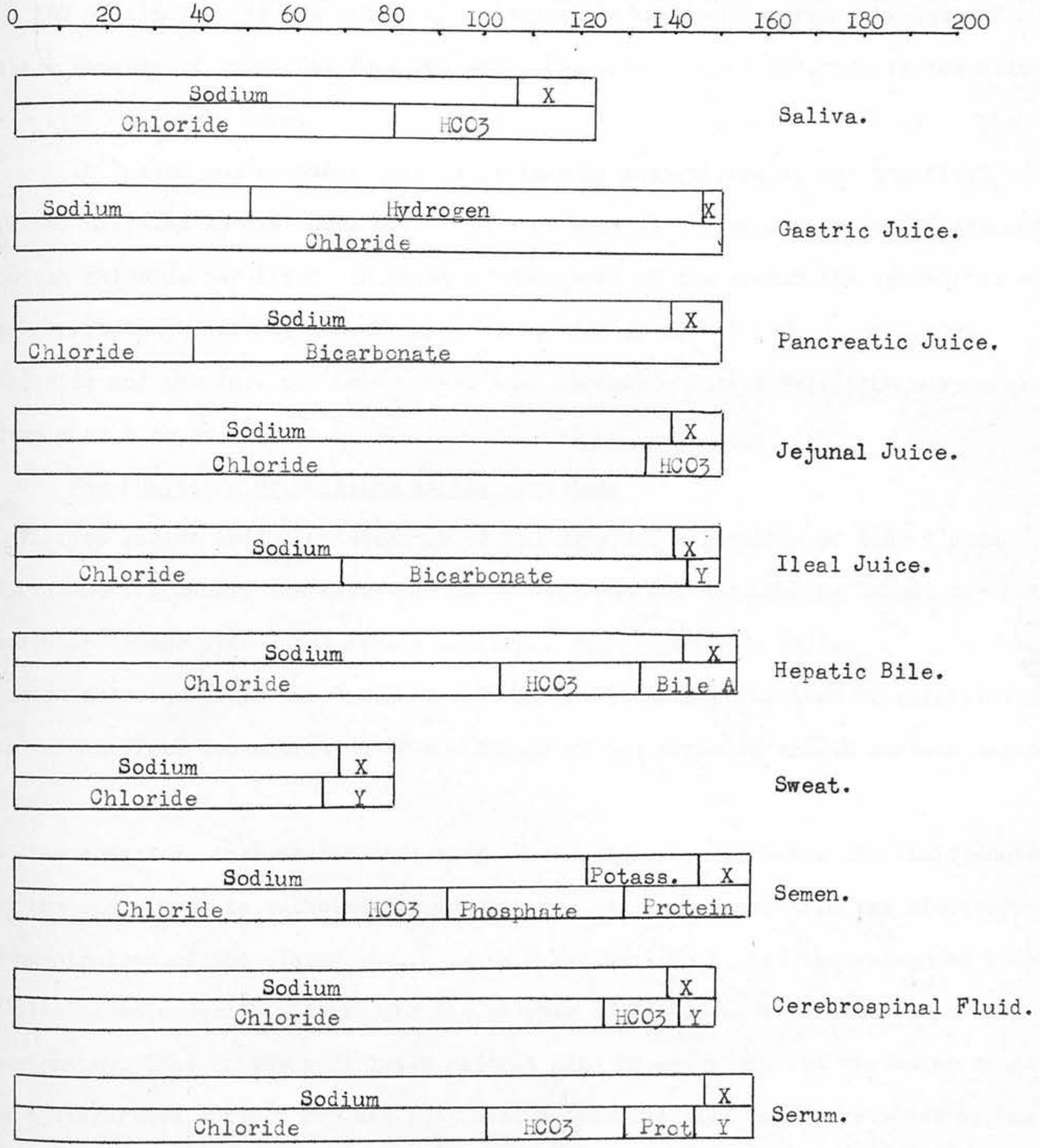
Composition of Certain Body Fluids Expressed Diagrammatically in Milli Equivalents per Liter.



It will be noticed that each fluid contains acidic and basic ions in equal proportions and that the secretions of the alimentary tract are approximately isotonic with the blood serum.

The urine contains varying amounts of chlorine, depending on the excess to be excreted to maintain or restore the concentration of chlorine in the body fluids at an optimum level. thus the urine may contain as much as 2% of sodium chloride or 340 millimolar. If the intake of chlorides is minimal or after the loss of large amoumts of chlorides from the body, the excretion of chloride in the urine may sink to nearly zero.

In faeces the chlorine loss is ordinarily insignificant, but the fluid faeces excreted in diarrhoea may contain as much as the equivalent of I5 grs. of sodium chloride per liter. In cases of carcinoma of the rectum the secretions of the irritated bowel and tumour may contain even up to 0.4 or 0.5% of sodium chloride and the loss may be so great that serious chloride depletion may result from such a cause.

The Functions of Chloride in the Organism.

I. Chlorides assist in the maintenance of the physical neutrality of body fluids.
2. Influence profoundly the distribution of water in the circulating blood, the intercellular tissue spaces and serous cavities, and in the body cells.
3. Sodium chloride plays the dominant role in the necessary function of maintaining the electrolyte concentration of the fluids of the organism within certain narrow limits.
4. Sodium chloride, through its influence on the kidneys, regulates the fluid content of the body. Even in pathological conditions the kidneys maintain the electrolyte concentration of the plasma within certain narrow limits, and the volume of body fluids is secondarily altered for the purpose of adjusting this electrolyte concentration. Thus if the body loses salt it also loses water, and the water drunk by a dehydrated subject who has lost sodium chloride will not be retained by the kidney unless salt also is ingested.

Sodium chloride Metabolism under Abnormal Conditions of Intake, of Loss, and in Diseased States.

The normal sodium chloride intake varies considerably, both with the diet itself and with the habits of the individual. A person using little extra table salt may ingest daily less than 5 grs. of sodium chloride, while another with a liking for highly seasoned foods may absorb as much as 20 grs. The daily excretion of sodium chloride in the urine, faeces and perspiration approximates closely to the intake, so that the normal adult maintains salt balance.

Expressed in terms of sodium chloride the normal concentration in the plasma of chlorine varies from 560 to about 625 mg. per 100 cc. Concentrations in the neighbourhood of 580 mg. per 100 cc. are frequently found in the plasma of healthy adults. For any given individual the concentration of sodium chloride in the plasma shows minor variations during the day which are related to meals. There is a slight but definite post-prandial fall, the result of the secretion of chloride rich digestive juices into the gastro-intestinal tract. With reabsorbtion of the secreted chlorides the plasma chloride concentration returns to the resting level.(49).

Numerous investigators (50, etc,) have shown that on chloride free diets the rate of excretion of chlorides in the urine falls until only minimal amounts are excreted daily (less than one quarter of a gram) and that at the same time the plasma sodium chloride concentration falls to approximately 560 mg.% and thereafter remains stationary for considerable periods. This plasma sodium chloride concentration of about 560 mg.% has been called by Ambard the "threshold point" forchloride excretion. In different individuals this "threshold point" is not always 560 mg.% but it forms a convenient and approximately correct figure for the healthy adult. It will be seen from an examination of the data of the experiments discussed later that healthy adults continue to excrete definite though small quantities of chloride in the urine when their plasma sodium chloride concentration is considerably below the so-called "threshold point", and Bartlett has shown that the sick patient may excrete very considerable quantities of chloride in the urine with plasma sodium chloride concentrations as low as 500 mg.% (Personal communication). From the evidence at hand therefore it can be said that there is no real threshold point for the excretion of chlorides by the kidney, such as, for instance, there is for the excretion of glucose; the considerable reduction in the excretion of chlorides in the urine when the plasma sodium chloride concentration falls below approximately 560 mg.% is due more probably to the necessity for conserving sodium in order that the osmotic pressure of the extracellular fluids may be maintained.

The Changes which occur in Body Electrolytes from the Loss of the Secretions of the Gastro-Intestinal Tract.

The loss of gastro-intestinal secretions which occurs in vomiting, from biliary or intestinal fistulae, in the copious stools of cholera, colitis etc. profoundly alters the concentration of electrolytes in the body fluids. Similarly, the serous or sero-sanguinous discharges which frequently accompany tumours in the left half of the colon, for example carcinoma of the rectum and polyposis of the colon, may seriously deplete the electrolytes of the body and endanger life. These abnormal losses frequently occur in diseased states which are essentially surgical problems, and have effects which may kill the patient or seriously jeopardise the result of the most skilful surgical intervention.

The secretions of the gastro-intestinal tract, with the exception of the saliva, are practically isotonic with the blood plasma. They also are of large volume and are normally reabsorbed in the lower reaches of the small bowel and right colon. Table 9 which is copied from Rowntree and McQuarrie (5I & 52) gives an indication of the large volumes of the digestive juices which are secreted by an adult man in 24 hours.

TABLE 9.

Secretion.	Volume in c.cm. in 24 Hrs.	Authority.
I. Saliva.	I500.	Bidder and Schmidt.
2. Gastric Juice.	2000 - 3000.	Bidder and Schmidt.
3. Bile.	300 - 500.	Pfaff and Balch.
4. Pancreatic Juice.	500 - 800.	Wohlgemuth.
5. Succus Entericus.	3000.	Pregl.
	Total 8000.	

Since the various digestive juices differ considerably in composition, the effects of obstruction of the oesophagus, at the pylorus, in the duodenum below the ampulla of Vater, and low down in the small intestine will vary considerably both in the electrolyte composition and in the actual volume of the fluid lost. Assuming that, in obstruction at thses various levels all the digestive juices are lost, I have constructed the following table to show both the fluid losses and the and the losses of electrolyte which occur if the obstruction is complete.

TABLE IO.

Level of Obstruction.	Vol. of Fluids Lost 24 Hrs.	Grs. Electrolytes Lost 24 Hrs.	Effect on Alkali Reserve.
In Oesophagus.	I500.	Na. 3.73. Cl. 4.26. HCO_3. 3.78.	Slight tendency towards acidosis.
At the Pylorus.	4500.	Na. 7.I8. Cl. 20.24. HCO_3. 3.78.	Definite tendency to alkalosis.
In the Duodenum below the Ampulla of Vater.	5800.	Na. II.37. Cl. 23.I7. HCO_3. I0.27.	Tendency to alkalosis.
Low down in the Small Intestine.	8800.	Na. 21.03. Cl. 37.33. HCO_3. I3.II.	Should cause very little change.

It will be seen from this table that the losses, both of water and of electrolytes, from intestinal obstruction may be very great and profoundly affect the water and electrolyte content of the body. The following table copied from McCance (53) shows the changes which occur in actual clinical cases in the alkali reserve, plasma Cl concentration, plasma Na concentration etc. from various causes.

TABLE II.

	Red Blood Cells Mil/c.mm.	Plasma Proteins %.	Blood Vol. c.cm.	Serum Na. mg./I00 c.cm.	Serum Cl. mg./I00 c.cm.	Alkali Reserve Vols.%	Blood Urea mg./I00 c.cm.	Acid Base Balance.
Normal.	5.0	7.0	5000	330	370	60	30	Normal.
Pyloric stenosis.	5.5	7.6	4500	3I5	300	90	50	Alkalosis.
Diarrhoea severe	6.0	8.2	4000	300	330	I5	I20	Acidosis.
Intestinal obstruction.	5.8	7.3	4200	290	320	40	80	Generally normal.
Sweating with no drinking.	8.0	9.0	3800	380	4I0	70	80	
Sweating with drinking.	6.5	7.9	4200	290	322	59	70	

These findings are common knowledge today, and it is interesting and instructive to realise that over a hundred years ago in 1831 certain of the essentials of this knowledge had been learnt by one who applied to the study of medicine a logical and deductive intelligence. Dr. W.B.O'Shaughnessy of Newcastle - upon - Tyne in a brief letter to the London Medical Gazette summarised the changes in the blood of patients suffering from cholera as follows:

1."The blood drawn in the worse cases of the cholera is unchanged in its anatomical or globular structure.

2. It has lost a large proportion of its water, 1000 parts of cholera serum having but the average of 850 parts of water.

3. It has lost also a great proportion of its neutral saline ingredients.

4. Of the alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.

5. Urea exists in the cases when suppression of urine has been a marked symptom.

6. All the salts deficient in the blood, especially the alkali or carbonate of soda, are present in large quantities in the peculiar white dejected matters."

Dr.O'Shaughnessy then passes from the changes which he observed in the blood of such cholera patients to the therapeutics which are logically demanded by such alterations of blood chemistry. He states that the cure is dependent on two principles: " First, to restore the blood to its natural specific gravity (i.e. its water content); second, to restore its deficient saline matters." He then says that, " the first of these can only be affected by absorbtion, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks,with sufficiently obvious modifications, apply to the second..........In severe cases copious enemata of warm water, holding the natural salts of the blood in solution are strongly recommended.....When absorbtion is entirely suspended theauthor recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood."

Karl Schmidt in 1850 confirmed and greatly amplified the analytical results of O'Shaughnessy. But, except for scattered and infrequent references, it was not until 1909 that O'Shaughnessy's principles were applied to the treatment of cholera by Rogers, and Nichols and Andrews, who used intravenous saline injections and decreased remarkably the mortality from the disease.

In forced losses of gastro-intestinal secretions from the proximal end of the alimentary tract the same changes of concentration of the blood, decrease in the plasma chloride concentration, rise in the blood urea and dehydration occur,as in cholera, but instead of acidosis there is an increase in the alkali reserve of the blood. In 1912 Hartwell and Houget (54) observed clinically, that life in cases of acute obstruction could be prolonged by saline injections and they attributed the effect of the saline chiefly to the relief of dehydration by the water in the solution. This clinical observation of Hartwell and Houget was lost sight of until McCallum (55) described the fall in blood chloride in cases of intestinal obstruction. Tileston and Comfort (56) described the rise in non-protein nitrogen, and McCann (57) the increase in the carbon di-oxide content of the blood. These findings have since been corroborated by a large number of clinical and experimental investigations, among which are valuable papers by Hastings, Murray and Murray (58), Haden and Orr (59), Gamble and Ross (60), and Hartmann and Smyth (61).

At the same time it was demonstrated by McCallum (55) and Haden and Orr (59) that these characteristic blood changes could be prevented and life prolonged by the administration of adequate amounts of isotonic salt solution.

It thus is instructive to reflect that the almost commonplace knowledge of today of the blood changes which occur when the secretions of the alimentary tract are lost to the body, was discovered more than a century ago by O'Shaughnessy, and that the therapeutics of today were advocated by him in 1831.

Abnormal Losses of Sodium Chloride Caused by Sweating.

R.A.McCance (62) in a most valuable series of experiments produced severe sodium chloride deficiency in normal subjects on a salt free diet by causing them to sweat profusely in a radiant heat bath. By special arrangements the sweat was collected and analysed. Enormous amounts of perspiration were secreted by this method. In a two hour period as much as 3200 cc. of perspiration containing 7.7 grs. of salt was lost, and amounts up to 40 and 50 grs. of salt were lost over a number of days.

McCances subjects were allowed to drink as much water as they wished and he considers that the symptoms produced were therefore those of sodium chloride deficiency alone. From his data and our own observations the following are the main symptoms and signs of sodium chloride defiency.

1. Loss of weight.

2. The appearance of the subject is considerably altered. The temporal hollows become accentuated and the cheeks and eys fall in. They become definitely ill and tired looking.

3. The sence of taste and flavour is affected. In one cases this aberration was interpreted as thirst but drinking large quantities of water afforded no relief. McCance noted that "even cigarettes had no taste". However, the difference between an apple and a pear remained obvious. It therefore seems that the sense of taste is more blunted than abolished. Washing out the mouth with salt water is often very refreshing and seems to improve the sense of taste.

4. Anorexia and nausia may be prominent symptoms. Actual vomiting may occur. This occured in D.W. in McCance's series and in R.W., S.T. and G.W., in mine. There was no actual complaint of indigestion in my cases and the nausia seemed unrelated to food. There was no constipation. In McCance's series the histamine response of the stomach was unaltered.

5. There is no interference with sleep.

6. The normal diuresis which follows the drinking of large quantities of water is frequently markedly delayed, and often occurs at night.

7. Cramps in the muscles are a prominant symptom, and are induced in a muscle group by any voluntary movement. In McCance's series coughing produced cramps all round the chest; yawning produced cramps in the floor of the mouth; voluntary movement of the fingers produced cramps in the muscle groups used. In my series the characteristic situations were in the muscles of the abdominal wall; in the calf muscles; and in the neck and shoulder regions. These cramps did not appear usually until the plasma sodium chloride concentration had been reduced to below 450 mg. %. In the case of G.W. they were severe enough to prevent him making any voluntary movement because

of the fear of inducing them. In his case also it is interesting to record that the pains were especially severe when his plasma sodium chloride concentration was between 408 and 330 mg.% and that in the twelve hours preceding the onset of the induced water intoxication he complained much less. These cramps are obviously the same as those investigated by Moss (63), Derrick (64), and Talbott and Michelsen (65), in miners and stokers, which these authors showed were caused by sodium chloride defiency, the result of excessive sweating, and which are completely controlled by drinking salt water.

8. Fatigue and a sense of exhaustion and weakness are characteristic of sodium chloride defiency. McCance found that he was unable to walk up stairs without breathlessness and great effort. In my cases, when the plasma sodium chloride concentration had been reduced to about 450 mg.% it was always necessary to transport the experimental subjects to the weighing machine in a wheeled chair. R.W. fainted after walking a few yards when his plasma sodium chloride concentration had been reduced to 384 mg,% and G.W. was unable to stand at all when his had been reduced to 330 mg.%. One of the most dramatic effects of the administration of sodium chloride to patients or experimental subjects with low plasma sodium chloride concentration is the rapid return of the sense of physical well being and vigour. This was especially marked in G.W., and it must be within the experience of every surgeon to have seen the astonishing return to apparent health which is made by subjects with low plasma chloride concentration after they have received saline solution intravenously.

9. The mentality is dulled. Questions are answered slowly or may even be forgotten before an answer can be elicited. Apathy may be present in many cases. Bartlett (Personal communication) has noticed that with the return of the plasma NaCl level towards the normal that such subjects have apparently a period of euphoria and elation. Often these subjects are extremely witty for a day or two when their blood chlorides ahve been restored to normal.

10. McCance noticed no change in the resting pulse rate, but a very marked fall in the pulse pressure. I noticed the same sign. It was for instance difficult to obtain blood samples because the veins failed to fill readily after the constricting band

had been placed around the arm.

These then are the main symptoms and signs of hypochloraemia. Loss of weight; sunken eyes and hollow cheeks; loss of the sense of taste; anorexia and nausia and even vomiting; delayed diuresis following the intake of water; muscular cramps; fatigue and weakness; impaired mentality and coma; and diminution in the pulse pressure; all often features of the clinical picture of intestinal obstruction, summer diarrhoea, cholera, or the weariness which assails those who live in the tropics.

The effects of severe sweating have been discussed in some detail because of the completeness of McCance's experiments and the remarkable confirmation of the clinical results of reduction of the plasma sodium chloride concentration which Bartlett's clinical cases and my experimental subjects afford. The minor symptoms of fatigue, lassitude, and mental impairment which are often present in normal subjects during hot weather are mainly the result of the loss of sodium chloride in the excessive sweating of the summer time and may be remidied by increasing the intake of salt.

Less Common Causes of Sodium Chloride Insufficiency.

In diabetes mellitus and diabetic coma there are abnormally low blood sodium and blood chlorine concentrations. The low blood sodium concentration is probably due to the fact that in the presence of acidosis there is a considerable loss of fixed base from the extracellular fluids. The fixed base lost is mainly sodium and, were it not that in diabetes mellitus the ability of the kidney to form and excrete ammonia is unimpaired, the loos of sodium and consequently of chloride, would be even more marked than it is. The effect of this sodium deprivation is seriously to reduce the electrolyte osmotic pressure of the extracellular fluids although the total osmotic pressure of the body fluids is high from the high concentration of sugar. If the concentration of sugar is the same, or nearly so, in all the body fluids, the distribution of water between the cells and extracellular fluids will mainly be effected by the electrolyte osmotic pressure; and, as the effective electrolyte osmotic pressure of the extracellular fluids is mainly caused by sodium (in spite of the ammonia deffense mechanism of the kidney, Blum and others have stated that as much as 40 to 50% of the body sodium may lost in diabetes mellitus) the osmotic pressure of the extracellular fluids will be reduced in comparison with the intracellular osmotic pressure mainly due to potassium, and water will pass into the cells. This hydration of the cells will of course be only relative to the extracellular fluids because in diabetes mellitus there is actually dehydration of the whole body from the forced diuresis which results from the excretion of the glucose in the urine. The net effect, however, of both the forced diuresis and the low plasma sodium concentration, is to reduce the volume of extracellular fluid, including the circulating blood, which plays an important part in the shock like condition of diabetic coma and is demonstrated by the concentration of the plasma proteins and haemoglobin in the blood.

Because of the loss of sodium there is also marked loos of chlorides as is shown by the great reduction in the plasma chlorine concentration in coma.(66, 67, 68.) Indeed, plasma chlorides tend to move inversly with the blood sugar in experimental and clinical diabetes (69), and even in non-diabetic animals (70).

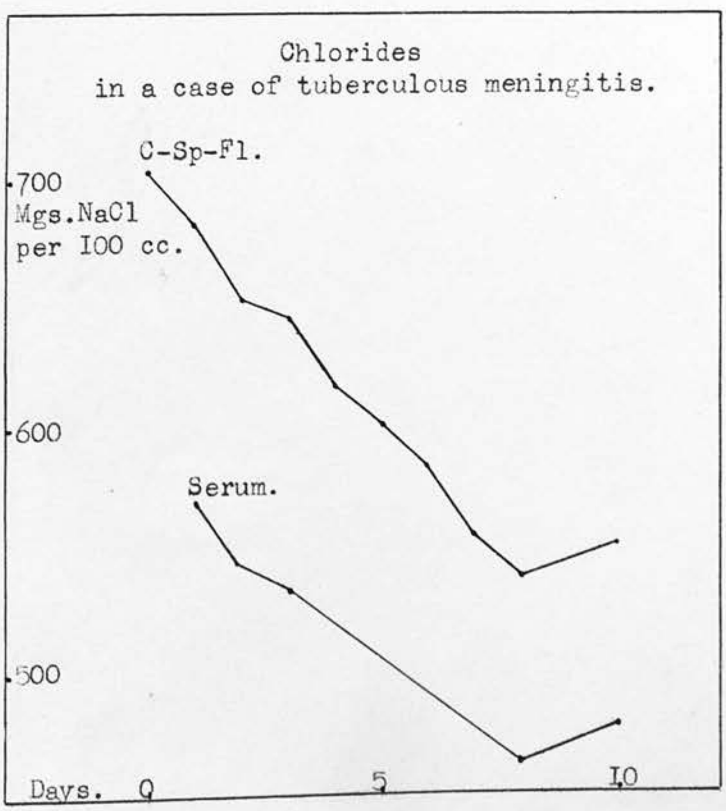
<u>Addison's Disease</u> is another condition in which the normal chemistry of the body fluids is profoundly altered. The disease is characterised by low serum sodium and clorine concentrations, a reduction in the alkali reserve, and a high plasma protein concentration, the blood volume is lowered and the red cell count is increased. The blood sugar falls, the serum potassium rises, and there may be some interference with the absorbtion of fat from the intestine. The blood urea rises. As the result of these changes in the normal chemistry of the body the expected alterations in the distribution of water occur. Extracellular fluid volume is reduced, intracellular increased, or, the same changes which occur when sweating is severe and accompanied by the ingestion of large amounts of water i.e., sodium chloride defiency without water deprivation. The primary cause is the same, loss of sodium and with it of chloride, and the benefits which result from sodium administration afford striking confirmation. In Addison's Disease the urine is the channel through which body sodium is lost, and, as a working hypothesis, it has

been suggested that the supra-renal cortex secretes a hormone which raises the renal threshold for sodium. In the absence of this hormone, sodium is swept out of the body in the urine, and the clinical picture of Addison's disease develops so strikingly similar in essentials to that of sodium chloride defiency produced by sweating without water deprivation.

It is not the purpose of this paper to discuss all diseases associated with alterations in the concentration of sodium chloride in the body. However, tuberculous meningitis does require notice because it illustrates an important principle which later will be stressed when the rationship between the concentration of chlorides in the plasma and the total chloride content of the body is discussed.

Tuberculous Meningitis is a disease which among many other features clinical, bacteriological, and biochemical, is characterised by a fall in the sodium chloride concentration of the cerebro spinal fluid. This is due to a progressive fall in the chloride concentration of the blood plasma, and the decrease in the concentrations of chloride in both plasma and cerebro spinal fluid is similar. This is well shown in the accompanying chart copied from "The Cerebrospinal Fluid, by H.Houston Merritt and Frank Fremont-Smith, 1937, W.B.Saunders Company.(71).

A comparison of the chloride content of the serum and the cerebrospinal fluid of a patient with tuberculous meningitis.



This parallelism in the progressive falls of the concentrations of sodium chloride in both blood plasma and cerebrospinal fluid illustrates the important principle that, in the higher concentrations of sodium chloride in the body, the chlorine ion can flow freely from one body fluid to another.

CHAPTER 6.

EXPERIMENTAL SODIUM CHLORIDE DEPLETION AND REPLACEMENT IN MAN.

Certain of the theoretical considerations concerning chloride metabolism have been discussed. It has also been pointed out that depletion of body chlorides occurs in certain diseases, as the result of vomiting, diarrhoea, excessive perspiration etc. In spite of the daily use of sodium chloride solution and its great clinical importance, its administration is still haphazard. It is only rarely that the correct amount of salt is given to patients whose body chlorides have been depleted by disease. Frequently too much salt is given. The excessive administratin of sodium chloride carries with it the risk of producing generalised oedema, with its special complication, pulmonary oedema. It must be within the experience of many surgeons to have seen oedema develop in the dependent parts of the body of patients who have received sodium chloride solution intravenously. On the other hand, probably, patients with hypochloraemia more frequently receive inadequate amounts of salt and the electrolyte concentration therefore of their body fluids is not restored to that concentration which is considered to be ideal. Because of this unsatisfactory state of affairs, it was decided to attempt to correlate the degree of the reduction of plasma chloride concentration with the amount of chloride which had been lost by the body; and conversly, in subjects with hypochloraemia, to correlate the increase in the concentration of chlorides in the plasma which results from the administration of sodium chloride, with the weight of this salt administered.

It has been seen that the chloride ion tends to distribute itself throughout all the body fluids, its concentration in extracellular fluids being in man, probably nearly double that in the intracellular fluid. This being so Bartlett and I have postulated that the chloride ion flows with comparative freedom from one body fluid to another. This probably is absolutely true for the migration of the chloride ion between subdivisions of the extracellular fluid. It will be remembered that in tuberculous meningitis there is a progressive fall in the chlorine concentration of the blood plasma and of the cerebrospinal fluid and that the two run parallel. White and Bridge (72) also showed in dogs that depletion of plasma chlorides by vomiting from intestinal obstruction was accompanied by a fall in the chlorine content of the tissues. It seems reasonable to postulate therefrom that there is a similar parallelism between the reduction in the blood plasma chloride concentration and that of the interstitial fluid and body as a whole when chloride is lost.

It is probably incorrect to postulate that a decrease in the concentration of chloride in the extracellular fluid will be accompanied by a proportionate decrease in its concentration in the intracellular fluid. The interposition of the cell membrane and the many factors which affect the distribution of water and chloride between the cells and extracellular fluids must invalidate such a simple direct relationship.

However, as a preliminary working approximate, we decided to assume that the chloride ion flows freely from one body fluid to another, and from this assumption, the following "formula" was developed.

Preliminary Considerations.

I. The percentage chlorine composition of the human body is 0.15% of the total body weight (47). A 70 Kg. adult will therefore contain 70 x.15% x 1000 = 105 grs. of chlorine in his body. Clinically, it is the custom to express the chlorine content of body fluids, such as blood plasma, in terms of milligrams of sodium chloride per 100 cc. This practise is far from scientific and carries with it numerous drawbacks, but, for the purposes of this paper it will be followed. Therefore, in terms of sodium chloride, the body of an adult weighing 70 Kg. will contain 105 x 1.65 = 173.25 grs. of sodium chloride, and, if all the chlorine in the body is combined with sodium, the percentage sodium chloride composition of the human body is 0.15 x 1.65% = 0.2475 per cent.

2. The concentration of sodium chloride in human plasma varies from 560 to 630 mgs. per 100 cc. For the purposes of the "formula" we considered 560 mgs. per 100 cc. of plasma to be normal.

3. If the concentration of chlorine in the blood plasma is a true reflection of its concentration in all the other fluids of the body, then a given percentage alteration from the normal concentration in the plasma should be accompanied by a similar

percentage alteration in the concentration of chlorine in the other body fluids, and also a similar percentage alteration in the total chlorine content of the body.

From these considerations, knowing the weight of the patient and the concentration of the plasma chlorides after depletion, it should be possible to restore the chlorine content of the body, and therefore the concentrations of the plasma chlorides to normal as follows;

Grs. of NaCl needed = Normal salt content of the body x % depletion of body chlorides.

$$= \frac{0.2475}{100.} \times \text{Wt. in Gms.} \times \frac{560 - \text{Depleted plasma NaCl concentration}}{560}$$

$$= 0.002475 \times \text{Wt. in Gms.} \times \frac{560 - C}{560}$$

Where C is the patients depleted Plasma NaCl concentration.

$$= 0.00000442 \times \text{Wt. in Gms.} (560 - C) \text{ .... I.}$$

From this preliminary formula several others have been developed.

Many patients come under the care of the surgeon both dehydrated and with depleted chlorides. Frequently their original body weight is not known. Consequently, to apply the above formula accurately it is necessary to calculate the patients original weight from his weight on admission. It will be remembered that patients showing symptoms and signs of dehydration have lost at least 6% of their body weight in fluids alone. Therefore:

The dehydrated body weight = Hydrated Weight - 6% of the Hydrated Weight.

= 94% of the hydrated weight.

and Hydrated Weight = Dehydrated Body Weight x $\frac{100}{94.}$

= 1.064 x Dehydrated Body Weight.

Applying this hydration factor in Formula I we have:

Gms. of NaCl needed = 0.00000442 x 1.064 x Dehydrated Weight (560 - C).

= 0.00000473 x Dehydrated Weight in Gms. (560 - C)....... 2.

Formula 2 is theoretically more accurate than formula I for patients who come under the care of the surgeon in a dehydrated condition with depleted body chlorides and should be used in clinical cases.

From it two further formulae have been developed by substituting (A) Body weight in pounds for body weight in grams and (B) Cubic Centimeters of 0.9% sodium chloride solution for Grms. of NaCl needed.

A. Gms. of NaCl needed = 0.002146 x Dehydrated Weight Pounds (560 - C)..... 3.

B. Cc. 0.9% NaCl sol. needed = 0.2385 x Dehydrated Weight Pounds (560 - C).. 4.

These formulae are unfortunately not easily remembered and therefore several clinical approximations have been evolved.

W.G.Maddock suggested that patients with hypochloraemia should receive: "0.5 Gms. of NaCl per Kilo of body weight for every 100 mg.% that the plasma NaCl concentration needs to be raised." This approximation gives a small excess of sodium chloride but it has been found to be a very useful clinical rule.............. 5.

I have suggested two other clinical approximations the first being derived from Maddock's rule.

1. That patients with hypochloraemia should receive 0.25 Gms. of NaCl per pound of body weight for every 100 mg.% that the plasma sodium chloride concentration needs to be raised to restore it to the normal of 560 mg.%. By this rule the patient receives a slightly greater excess than by Maddock's rule................. 6.
2. That patients with hypochloraemia should receive 25 cc. of 0.9% sodium chloride solution per pound of body weight for every 100 mg.% that the plasma sodium chloride concentration needs to be raised to restore it to the normal of 560 mg.% By this rule the patient receives a slight excess of sodium chloride but this excess is not so great as that given by Maddock's rule............................ 7.

The following table illustrates the differences in the amounts of sodium chloride which would be given by the various formulae to a patient weighing 50 Kg. and whose plasma sodium chloride concentration is 460 mg.%

TABLE 12.

By Formula.No.	Gms.NaCl given.	cc.0.9% NaCl sol.given.
No.2. Optimal amount NaCl required.	23.65.	2628.
No.3. Amount of NaCl given.	23.606.	2623.
No.4. Amount of NaCl given.	23.606.	2623.
No.5. Amount of NaCl given.Maddock's rule.	25.0.	2778.
No.6. My first rule e 0.9% NaCl Sol.B.P.	27.5.	3056.
e 0.85% NaCl Sol.U.S.P.	27.5.	3235.
No.7. My second rule e 0.9% NaCl Sol.B.P.	24.75.	2750.
e 0.85% NaCl Sol.U.S.P.	23.38.	2750.

Such clinical rules can be multiplied almost indefinitely but it will be seen from the table that if the optimal amount of NaCl required by this patient was 23.65 grams any of the clinical rules given may be applied and the margin of error will be small. Maddock's rule is probably the most satisfactory for surgeons who are accustomed to having the weights of their patients recorded in kilogrammes, and my first rule is sufficiently close for use by surgeons whose patients weight is recorded in pounds. But, whatever formula isused, for satisfactory results the weight of the patient on admission and also the composition of the sodium chloride solution administered must be accurately known. Using formulae 3 and 4 the accompanying tables have been constructed to simplify the administration of sodium chloride to patients with hypochloraemia. Table I3 gives the ideal weight of NaCl required and Table I4 the ideal volume of NaCl solution of strength equal to 0.9% which will require to be administered. (Pages 73 and 74).

Plasma sodium chloride concentration in milligrams per cent.

	540	520	500	480	460	440	420	400	380	360	340	320	300
lbs. 5	0.2	0.4	0.6.	0.9	I.I	I.3	I.5	I.7	I.9	2.2	2.4	2.6	2.8
I0	0.4	0.9	I.3	I.7	2.2	2.6	3.0	3.4	3.9	4.3	4.7	5.2	5.6
I5	0.6	I.3	I.9	2.6	3.2	3.9	4.5	5.2	5.8	6.4	7.I	7.7	8.4
20	0.9	I.7	2.6	3.4	4.3	5.2	6.0	6.9	7.7	8.6	9.4	I0.3	II.2
25	I.I	2.2	3.2	4.3	5.4	6.4	7.5	8.6	9.6	I0.7	II.8	I2.9	I3.9
30	I.3	2.5	3.9	5.2	6.4	7.7	9.0	I0.3	II.6	I2.9	I4.2	I5.4	I6.7
35	I.5	3.0	4.5	6.0	7.5	9.0	I0.5	I2.0	I3.5	I5.0	I6.5	I8.0	I9.5
40	I.7	3.4	5.2	6.9	8.6	I0.3	I2.0	I3.7	I5.5	I7.2	I8.9	20.6	22.3
45	I.9	3.9	5.8	7.7	9.7	II.6	I3.5	I5.5	I7.4	I9.3	2I.2	23.2	25.I
50	2.I	4.3	6.4	8.6	I0.7	I2.9	I5.0	I7.2	I9.3	2I.5	23.6	25.8	27.9
60	2.6	5.2	7.7	I0.3	I2.9	I5.5	I8.0	20.6	23.2	25.8	28.3	30.9	33.5
70	3.0	6.0	9.0	I2.0	I5.0	I8.0	2I.0	24.0	27.0	30.0	33.0	36.I	39.I
80	3.4	6.9	I0.3	I3.7	I7.2	20.6	24.0	27.5	30.9	34.3	37.8	4I.2	44.6
90	3.9	7.7	II.6	I5.5	I9.3	23.2	27.0	30.9	34.8	38.6	42.5	46.4	50.2
I00	4.3	8.6	I2.9	I7.2	2I.5	25.8	30.0	34.3	38.6	42.9	47.2	5I.5	55.8
II0	4.7	9.4	I4.2	I8.9	23.6	28.3	33.0	37.8	42.5	47.2	5I.9	56.7	6I.4
I20	5.2	I0.3	I5.5	20.6	25.8	30.8	36.I	4I.2	46.4	5I.5	56.7	6I.8	67.0
I30	5.6	II.2	I6.7	22.3	27.9	33.5	39.I	44.6	50.2	55.8	6I.4	67.0	72.5
I40	6.0	I2.0	I8.0	24.0	30.0	36.I	42.I	48.I	54.I	60.I	66.I	72.I	78.I
I50	6.4	I2.9	I9.3	25.8	32.2	38.6	45.I	5I.5	57.9	64.4	70.8	77.3	83.7
I60	6.9	I3.7	20.6	26.5	34.3	4I.2	48.I	54.9	6I.8	68.7	75.5	82.4	89.3
I70	7.3	I4.6	2I.9	29.2	36.5	43.8	5I.I	58.4	65.7	73.0	80.3	87.6	94.9
I80	7.7	I5.5	23.2	30.9	38.6	46.4	54.I	6I.8	69.5	77.3	85.0	92.7	I00.4
I90	8.2	I6.3	24.5	32.6	40.8	48.9	57.I	65.2	73.4	8I.5	89.7	97.9	I06.0
200	8.6	I7.2	25.8	34.3	42.9	5I.5	60.6	68.7	77.3	85.8	94.4	I03.0	III.6
2I0	9.0	I8.0	27.0	36.I	45.I	54.I	63.I	72.I	8I.I	90.I	99.I	I08.2	II7.2
220	9.4	I8.9	28.3	37.8	47.2	56.7	66.I	75.5	85.0	94.4	I03.9	II3.3	I22.8

TABLE I3.

Results to the nearest one tenth of a Gram.

Plasma sodium chloride concentration in milligrams per cent.

	540	520	500	480	460	440	420	400	380	360	340	320	300
s.5	20	50	70	I00	I20	I40	I60	I90	2I0	240	260	280	3I0
I0	50	I00	I40	I90	240	280	330	380	430	480	520	570	620
I5	70	I40	2I0	290	360	430	500	570	640	720	790	860	930
20	I00	I90	290	380	480	570	670	760	860	950	I050	II40	I240
25	I20	240	360	480	600	720	830	950	I070	II90	I3I0	I430	I550
30	I40	290	430	570	720	860	I000	II40	I290	I430	I570	I720	I860
35	I70	330	500	670	830	I000	II70	I340	I500	I670	I840	2000	2I70
40	I90	380	570	760	950	II40	I340	I530	I720	I9I0	2I00	2290	2480
45	2I0	430	640	860	I070	I290	I500	I720	I930	2I50	2360	2580	2790
50	240	480	720	950	II90	I430	I670	I9I0	2I50	2390	2620	2860	3I00
60	290	570	860	II40	I430	I720	2000	2290	2580	2860	3I50	3430	3720
70	330	670	I000	I340	I670	2000	2340	2670	30I0	3340	3670	40I0	4340
80	380	760	II40	I530	I9I0	2290	2670	3050	3430	3820	4200	4580	4960
90	430	860	I290	I720	2I50	2580	30I0	3430	3860	4300	4720	5I50	5580
I00	480	950	I430	I900	2390	2860	3340	3820	4290	4770	5250	5720	6200
II0	520	I050	I570	2I00	2620	3I50	3670	4200	4720	5250	5770	6300	6820
I20	570	II40	I720	2290	2860	3430	40I0	4580	5I50	5720	6300	6870	7440
I30	620	I240	I860	2480	3I00	3720	4340	4960	5580	6200	6820	7440	8060
I40	670	I340	2000	2670	3340	40I0	4670	5340	60I0	6680	7350	80I0	8680
I50	720	I430	2I50	2860	3580	4290	50I0	5720	6440	7I60	7870	8590	9300
I60	760	I530	2290	3050	3820	4580	5340	6II0	6870	7630	8400	9I60	9920
I70	8I0	I620	2430	3240	4050	4870	5680	6490	7300	8II0	8920	9730	I0540
I80	860	I720	2580	3430	4290	5I50	60I0	6870	7730	8590	9440	I0300	III60
I90	9I0	I8I0	2720	3630	4530	5440	6340	7250	8I60	9060	9970	I0880	II780
200	950	I9I0	2860	3820	4770	5720	6680	7630	8590	9540	I0490	II450	I2400
2I0	I000	2000	30I0	40I0	50I0	60I0	70I0	80I0	9020	I0020	II020	I2020	I3020
220	I050	2I00	3I50	4200	5250	6300	7350	8400	9440	I0490	II540	I2590	I3640

TABLE I4.

Results to the nearest I0 cc.

In order to substantiate or disprove the validity of these formulae, and to elucidate some of the clinical phenomena of chloride depletion and replacement it was decided to use normal subjects and to adapt the conditions of each experiment to the particular problem requiring clarification. Four normal healthy male subjects were used and the general outline of the experiments was as follows.

Each experiment was divided into three main periods.

I. A preliminary period on a chlorine poor diet.

2. A depletion period during which the body chlorine of the subject was depleted by continuous gastro-duodenal drainage.

3. A replacement period during which the body chlorine of the subject was restored to normal by the intravenous administration of 0.85% sodium chloride solution.

Details of the Preliminary Period.

I. Each subject was given a diet of adequate energy value but containing as little chlorine as possible for a number of days until he excreted less than one gram of sodium chloride per day in his urine. All determinations of urinary chlorides were made by the Volhard-Arnold method. The stool during this period was not collected.

2. The subject was weighed accurately at the same time every day under standard conditions of nudity, and after emptying the bladder.

3. Throughout the whole period of study i.e., preliminary, depletion and replacement periods, venous blood was taken daily for chemical analysis. It was not collected under liquid paraffin. The plasma chloride concentration was determined daily by the Wilson and Ball modification of the Van Slyke method (accurate to approximately I%)* All the results of chloride determonations were expressed in terms of milligrams of sodium chloride per IOO cc.of plasma. The CO_2 combining power of the plasma was determined freqeuntly.

In the third experiment on G.W. the blood Non-protein nitrogen was determined daily during the periods of chlorine depletion and replacement. In the fourth

* For all the chemical determinations I am indebted to Dr. Svend Pederson.

experiment on H.A. the blood non-protein nitrogen, and blood protein concentrations were also determined during the same periods. Only lack of adequate technical assistance precluded the daily estimation of blood potassium, sodium, calcium - both ionised and non-ionised fractions - the blood specific gravity, the haemoglobin concentration by gravimetric method, the red cell count and the osmotic pressure of the plasma, both total and that due to the blood proteins. The necessity for complete blood examination became more and more apparent as each experiment progressed, and I feel that in the near future, similar experiments should be carried out in which every possible source of information should be explored.

By this preliminary period on chloride poor diet the subjects were reduced to a common level of chloride excretion, and therefore presumably, if there are reserves of chloride in the body these were nearly exhausted by the time there was a daily excretion of less than one gram of sodium chloride in the urine. During this period a significant fall in weight occured but no important decrease in the concentration of sodium chloride in the plasma.

<u>Details of the Period of Chloride Depletion.</u>

I. When each subject was excreting daily less than one gram of sodium chloride in the urine, he was confined to bed in a room at a temperature of 72 F. and the chlorine content of the body was depleted by continuous gastro-duodenal drainage. This was effected by means of a Rehfuss tube passed through the nose into the stomach which was connected to a Wangenstein suction system with a trap bottle inserted into the system for the collection of the secretions. Nothing was given by mouth except distilled water in known amount, and a definite quantity of salt free candy to promote the secretion of saliva, provide some energy for the body, and to preserve the integrity of the mucous membranes of the upper gastro-intestinal tract. Naturally most of the water given by mouth and also some of the candy was sucked back by the Rehfuss tube thus losing a certain proportion of the calorific value of the candy. It was however assumed that 100 grams of the candy was absorbed daily both in the calculation of daily calorific intake and of the water of combustion of the candy. The errors so produced are small. The disadvantage of giving water by mouth did not affect the total chloride content of the gastro-duodenal secretins, concerning which only the total chloride content and volume required to be known. The analysis for chloride was made by the Volhard-Arnold method. The lack of adequate technical assistance precluded the extimation of sodium, potassium, bicarbonate etc. in the drainage fluid.

2. All the urine was collected and analysed for chloride by the Volhard-Arnold method. In both R.W., and S.T., no stool was passed during the period of study. In G.W., several liquid stools were lost after experimental water intoxication had been produced; and in H.A., a single stool weighing 207 grams was passed which was not analysed, but was presumed to contain only traces of chlorine.
3. The subject was accurately weighed and samples of blood were taken daily for chemical analysis.
4. A varying amount of 5% glucose solution was given daily by the continuous intravenous drip technique. The actual volume given depended on the amount of fluid which it was desired that the subject should receive.

Details of the Period of Chloride Replacement.

1. When a satisfactory low concentration of sodium chloride in the plasma had been achieved by the depletion period, sodium chloride in physiological salt solution was given intravenously in calculated amount to restore the concentration of salt in the body to normality. The replacement was carried out over periods of 24 to 48 hours, as will be detailed in each experiment.
2. Body weight, blood chemistry, urine analysis, etc. were estimated as previously described.
3. A maintenance chlorine poor diet was given.

Throughout the depletion and replacement periods it was extimated that each subject daily excreted through the skin 0.30 grams of sodium chloride. It is realised that this figure, 0.30 grams of NaCl, for the daily loss of salt through the skin is a mere approximation. It is based on the researches of Freyberg and Grant (73) who showed that, in two healthy adult men going about their daily work in the laboratory and taking precautions not to sweat, the average daily excretion of chloride, as sodium chloride, by the skin was 304 milligrams per day. Sweating in all four of our experimental subjects was minimal, and by using this approximation it is probable that the error introduced into each experiment was small.

Experiment I.

The first subject, R.W., was a healthy normal boy aged 18. Psychologically he proved excellent, and he was also a rapid loser of chloride. This is most probably because the gastric juice he secreted contained a high concentration of chloride. In the next experiment, on S.T., the subject was depleted much less rapidly because he secreted a gastric juice of low chloride content. Such differences may account for those observed clinically between cases which exhibit markedly differing plasma sodium chloride concentrations as the result of apparently the same duration and severity of symptoms from for instance, intestinal obstruction at the same level.

Table 15 on page 79 summarises the data obtained and figure 3 depicts graphically the weight loss, observed and calculated plasma sodium chloride concentrations, day by day. It will be seen that:

1. The observed and calculated sodium chloride concentrations agree closely during the depletion period. On the first day of the depletion period there is a difference of 16 mgs.%, the calculated being lower than the observed concentration. This difference is probably due to the fact that the subject lost 4185 cc. of water more than he received, assuming an insensible loss of water of 1200 cc. per day. Therefore there was a relative concentration of electrolytes in the body fluids, thus causing the observed plasma sodium chloride concentration to be higher than the calculated. On the second day the observed and calculated concentrations are practically identical, the difference between the intake and output of water being a loss of only 650 cc. On the third day, the observed plasma sodium chloride concentration was lower than the calculated by 24 mgs.%. This difference is due to two factors. The first is the relative hydration of the body fluids because of the fluid intake over the output of 260 cc. and the second factor is probably a combination of many. It appears that when plasma sodium chloride concentrations

case, S.T., we were able to account for this difference. Bartlett had noticed in clinical cases that, for a day or two after sodium chloride had been administered to a patient, he usually lost weight and the plasma sodium chloride concentration continued to increase without further administration of salt. This effect therefore is due probably to loss of water from the body with consequent concentration of body electrolyte, in order to bring the electrolyte concentration of his body fluids to the optimal level. The importance of such a dilution effect is obvious when it is realised that, on the first day of R.W.s replacement period he received 2550 cc. more fluid than he excreted, and on the second day 1024 cc. Probably therefore if R.W. had been studied for a further day his weight would have decreased and the concentration of sodium chloride in his blood plasma would have risen nearly to normal.

3. During the period of depletion there was a continual rise in the CO2 combining power of the blood. The extent of this increase indicates that probably more gastric than pancreatid juice was being removed.
4. During the period of hypochloraemia the losses of sodium chloride in the urine were minimal.
5. No stool was passed during the period of study.

Clinical Observations.

Preliminary Period. His only complaint was that the diet was insipid.

Depletion Period. During the depletion period he remained in bed and was not disturbed by the continual presence of the Rehfuss tube. He early showed signs of salt depletion and water loss - weakness, tiredness, pallor, hollow cheeks, poor pulse pressure, etc. and his mentality became much less keen. On the third day of the depletion period he complained of cramps in any muscle group on exertion, no doubt partly due to the existing alkalosis, and, while being transferred to the wheeled chair to be weighed he fainted. The total weight of sodium chloride lost was 35.535 grams. His observed plasma sodium chloride concentration was 384 mgs.%. At this concentration the calculated weight of sodium chloride required to restore his plasma sodium chloride concentration to normal was 44.30 Grs.

TABLE I5.

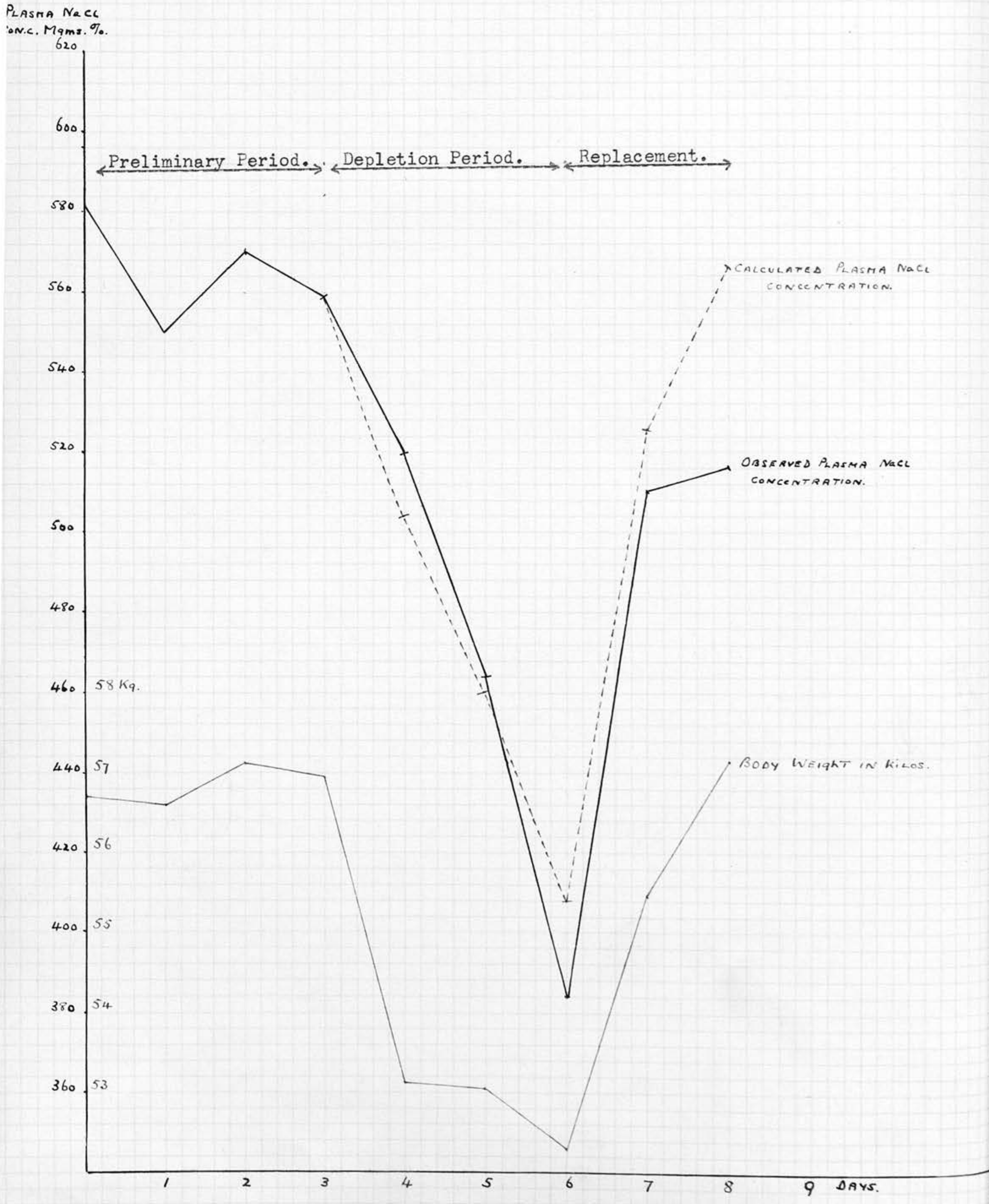
	Preliminary Period				Depletion Period			Replacement Period	
ate.November.	27	28	29	30	Dec.I	2	3	4	5
eight.	56.65	56.60	57.I3	56.95	53.I5	53.07	52.24	55.4I	57.I5
iet.(Calories.		3040	2790	3090	772	I204	I022	780	I540
iet.(NaCl Content.		I.I6	0.927	0.874	-	-	-	0.522	0.594
luids.(By mouth.		-	-	-	430	450	390	520	2370
					g	g	g	8	8
luids.(Intravenous.		-	-	-	I860	4020	3890	42I0	I264
rainage.(Volume.		-	-	-	30I5	2680	I980	-	-
rainage.(NaCl Content.					I2.995	I0.800	I0.II8	-	-
rine.(Volume.		2665	940	2390	2260	I240	840	780	I4I0
rine.(NaCl Content.		2.025	0.636	0.359	0.497	0.074	0.I5I	0.I64	I.I27
aCl Skin Loss.		0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
otal NaCl Loss.		-	-	-	I3.792	24.966	35.535	-	-
ifference Fluid ntake : Output.		-	-	-	4I85	650 4835	260 4575	2550 2025	I024 I00I
aCl Given.		-	-	-	-	-	-	35.785	I0.944
aCl Retained.		-	-	-	-	-	-	35.634	I0.350
alculated Plasma aCl Concentration.		-	-	-	504	460	408	525	566
bserved Plasma aCl Concentration.	582	55I	57I	559	520	464	384	5I0	5I6
lasma CO2 Comb.Power.	54	43.7	46.8	47.I	52.7	7I.2	75.I	67.0	63.6

Calculated Salt Content of the Subject I40.90 Grams.

of less than about 425 mgs.% are reached, further removal of chloride from the body produces a disproportionate fall in the plasma sodium chloride concentration. The causes are probably many but purely as a working hypothesis it is suggested here that below such plasma sodium chloride concentrations the intracellular chloride is very largely retained for the vital processes of the cells themselves and most of the chloride removed is lost by the extracellular fluids only.

2. During the replacement period there is less agreement between the observed and calculated sodium chloride concentrations especially on the second day. In the next

Russ Wickterman, aged 18. November 27 to December 5.



It was therefore decided to replace on the first day of the replacement period a weight of salt equal to that which he had lost, and 35.785 grs. were actually given and 35.634 grs. were retained. Since on the second day of his replaement period his plasma sodium chloride concentration had not returned to normal (partly for reasons outlined above) it was decided to give him an additional 8.606 grs., the difference between the amount of salt given the previous day and the calculated need of 44.30 grs. Actually 10.944 grs. were given and 10.35 grs were retained.

Replacement Period. Soon after the commencement of the administration of sodium chloride the improvement in his general condition was extremely marked. The cramps disappeared and his mental reactions became rapid and he even became somewhat euphoric. He was discharged in excellent physical condition.

Experiment 2.

The second subject, S.T., was a healthy normal man aged 20. Psychologically he was not so satisfactory as R.W. Also his gastric and duodenal secretions were of comparatively low chloride content and therefore, in spite of a considerable daily volume of drainage, reduction in the plasma sodium chloride concentration was slow. Table 16 on page 82 summarises the data obtained and Figure 4 depicts graphically the weight loss, observed and calculated plasma sodium chloride concentrations day by day. It will be seen that;

1. The observed and calculated plasma sodium chloride concentrations again agree closely with minor differences due to relative concentration or dilution of the body fluids.
2. The total sodium chloride loss was 35.265 grams which reduced the concentration of sodium chloride in the plasma to 435.6 mgs.%. The calculated amount of sodium chloride needed to restore normality was 39.9 grams. It was decided to administer the amount over a 48 hour period and on the first day, 27.210 Grams was given, 26.818 grs. of which was retained. By calculation this amount of sodium chloride should have raised the plasma sodium chloride concentration to 519 mgs.%, the actual level reached being 500 mgs.%. This discrepancy is again probably due to the excess of the fluid intake over the output of 2073 cc. thus producing a relative dilution of the body fluids

S.T.

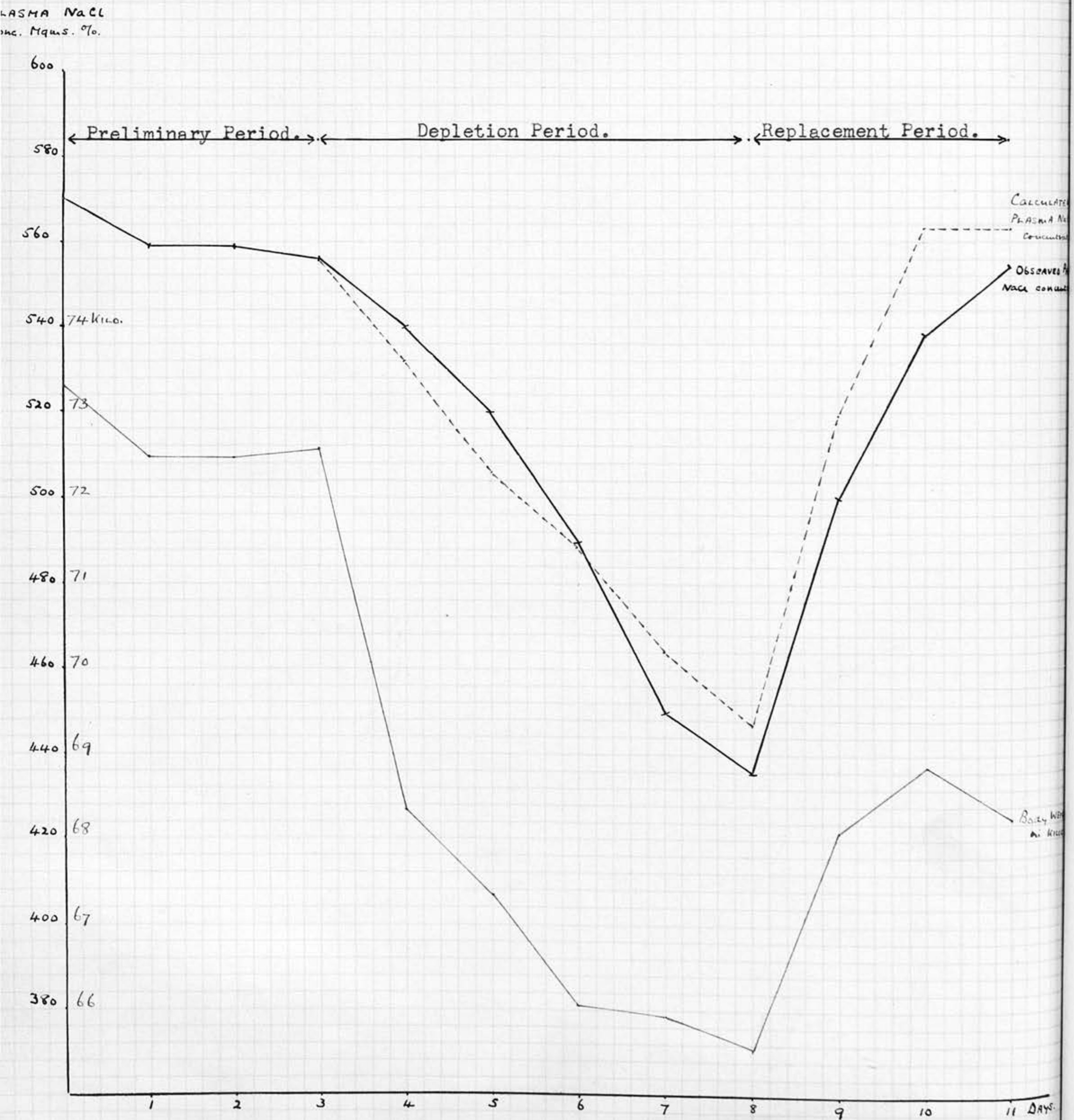
TABLE I6.

Dec.	Preliminary Period.				Depletion Period.					Replacement Period.		
	I0	II	I2	I3	I4	I5	I6	I7	I8	I9	20	21
t.	73.23	72.43	72.42	72.58	68.35	67.35	66.06	65.92	65.56	68.05	68.85	68.2I
Cals.	2900	2900	2900	2900	II20	II20	II20	II40	II20	I245	3088	29I2
NaCl.	I.359	0.704	I.393	I.069	-	-	-	-	-	0.664	0.469	0.506
(Mouth.	-	-	-	-	II20	950	I200	II60	II30	I200	I200	I200
(I.V.	-	-	-	-	g 3600	g 3600	g 3600	g 3700	g 3600	s 3I23	s I720	-
age (Vol.	-	-	-	-	2270	I620	2I00	I700	I055	-	-	-
(NaCl.	-	-	-	-	7.24I	7.857	6.383	6.324	4.I88	-	-	-
(Vol.	-	I330	990	I295	2845	2080	I390	I505	2I70	I050	II90	II48
e((NaCl.	-	0.878	I.030	0.544	0.256	0.I25	0.I39	0.090	0.I52	0.042	0.260	0.207
Skin	-	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
NaCl	-	-	-	-	7.797	I6.079	22.9II	29.625	35.265	-	-	-
rence In:Out.	-	-	-	-	I5I5	350 I865	II0 I755	445 I3I0	305 I005	2073 I068	530 I598	II48 450
Given.	-	-	-	-	-	-	-	-	-	27.2I0	I5.089	0.506
Retained.	-	-	-	-	-	-	-	-	-	26.8I8	I4.529	-
Plasma Conct.^{n}	-	-	-	-	532	506	485	464	447	5I9	564	564
rved a NaCl.	57I	559	558	556	540	520	490	449	436	500	538	554
Comb ^{g} r.	49.5	5I.6	55.3	58.6	59.0	59.2	58.6	63.2	67.3	68.4	62.3	56.3

Calculated Salt Content of the Subject. I79.64 Grams.

and diminution in the concentration of body electrolytes. On the second day a further I5.089 grams of salt was given, I4.529 of which was retained, making a total sodium chloride retention during the replacement period of 4I.347 grams. This sodium chloride retention by the end of the second day should have raised the plasma sodium chloride concentration to 564 mgs.% but again, owing to the hydration of the body by a further

Stanley Tesch, aged 20. December 10 to 21.



530 cc., the plasma sodium chloride concentration only reached 538 mgs.%. In the next 24 hour period, without further administration of salt, the subjects plasma sodium chloride concentration rose to 554 mgs.%, at the same time he lost 0.64 Kg. in weight and his body fluids were depleted of II48 cc. of water. It is reasonable therefore to state that the rise in plasma sodium chloride concentration was due to concentration of the body electrolytes produced by loss of fluid from the body. The variations therefore which many authors have noted in the concentration of body electrolytes are probably partly dependent on the volume of the body fluids at the time of the blood analysis.

3. As compared with R.W., there was not so marked an increase in the CO2 combining power of the blood plasma, indicating that a larger proportion of duodenal than gastric juice was being removed in his case.

4. The Urine. It is noteworthy that there was a marked fall in the volume of urine secreted after the administration of salt, and in spite of the large doses of sodium chloride given intravenously there was no significant increase in the weight of sodium chloride excreted. This effect has been repeatedly noticed, both in these experiments and by Bartlett and other clinical observers, and is due to the restoration of normal electrolyte concentration in the blood plasma. Subjects with depleted body electrolytes are unable to retain water if given alone or with glucose, because, if water were retained, they would lower unduly the osmotic pressure of the body fluids, especially the extracellular fluids. Occasionally such retention of water in the presence of depleted body electrolytes does occur; the reduction in the osmotic pressure of the extracellular fluids causes a transference of water into the cells. In the brain this occurence is serious as the cellular hydraemia causes a marked increase in the volume of the brain, and, if this increase is larger than the volume of cerebrospinal fluid which can be forced out of the skull, intracranial pressure rises rapidly and the clinical picture of increased intracranial pressure supervenes. This condition has been called water intoxication and was deliberately produced in the next experiment.

These observations emphasise the important fact that, in dehydrated patients with depleted body electrolytse, the administration of water alone or with glucose will not rehydrate them and may even be lethal, but water and electrolytes such as sodium chloride in solution in proper amount will effect both rehydration and the restoration of the normal concentration of body electrolytes. Conversely, if salt in hypertonic solution be given to dehydrated patients with hypochloraemia, only the weight of salt which can be retained in the body fluids to form a solution of normal osmotic pressure and chemical constitution will be retained. The excess of salt which cannot find body water to form such a normal solution will be excreted. In other words, the kidney will "spill" the weight of salt which the body fluids cannot assimilate to form a solution of normal osmotic pressure and chemical composition. This important fact is well demonstrated in the Replacement Period of experiment 3. Therefore, in actual clinical practise, it is useless to administer sodium chloride in solutions of higher concentration than that of normal physiological salt solution to restore the salt content of the body to normal.

Clinically the effects of this experiment were similar to those noticed in the experiment on R.W., except that the muscular cramps were not nearly so severe. All the typical signs and symptoms of salt deprivation were observed. At the end of the replacement period he also experienced a sense of wellbeing and was euphoric. He was discharged looking and feeling well.

Experiment 3.

The experiment conducted on G.W. proved itself to be of the very greatest interest. It is probably the first human case in which Water Intoxication was produced deliberately. He was a man aged 39 who had been a bank clerk until the depression and who has since been unemployed. Psychologically he proved himself an escellent subject. Table I7 summarises the data obtained and figure 5 depicts graphically the daily weight, observed and calculated sodium chloride concentration in the plasma. It will be seen that:

I. The observed and calculated plasma sodium chloride concentrations agree closely until a concentration of approximately 450 mgs.% was reached. During the first day G.W.

G.W.

TABLE I7.

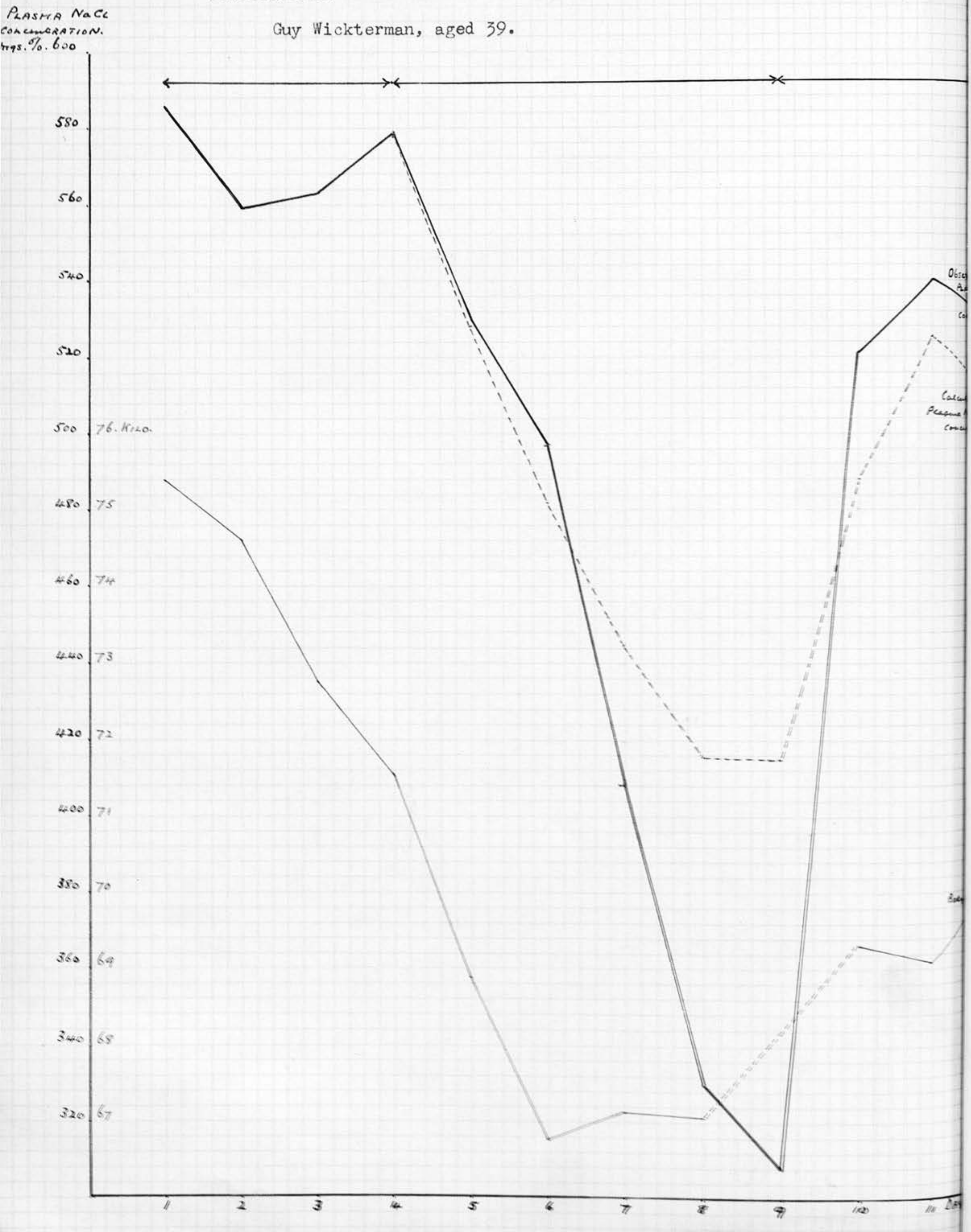
Jan.	4	5	6	7	8	9	IO	II	I2	I3	I4	I5
	Preliminary Period.				Depletion Period.					Replacement period.		
t.	75.39	74.6I	72.75	7I.53	68.84	66.76	67.I4	67.06	-	69.35	69.09	68.82
Cals.	2I59	2265	25I3	24I7	930	400	I052	99I	400	372	456	I853
NaCl.	0.536	0.759	0.932	0.22I	-	-	-	-	0.276	34.0	0.427	0.I22
(Mouth.	-	-	-	-	550	240	I200	II40	34I4	2000	925	I5IO
(I.V.	-	-	-	-	265Ig	-	3264g	2954g	-	(I860g (2750s (46IO	2677s	-
(Vol.	-	-	-	-	2760	2820	2I75	I980	-	-	-	-
age((NaCl.	-	-	-	-	I4.794	I3.592	II.006	8.989	-	-	-	-
(Vol.	I8I5	I990	I620	I860	I8IO	-	355	I20	8IO	I070	2570	I540
(NaCl.	4.99	I.8II	0.842	0.78I	0.56I	-	0.046	0.0I2	0.I05	0.235	I0.5II	3.989
Skin	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
NaCl	Preliminary Period Only.				Depletion Period Losses.							
	5.29	7.40I	8.543	9.624	I5.655	29.547	40.899	50.200	50.329	-	-	4.I67
ence In:Out	-	-	-	-	2659	3780 6349	734 56I5	794 482I	I404 2877	4340 I463	I68 I295	I230 65
Given.	-	-	-	-	-	-	-	-	-	57.37	22.755	-
Retained.	-	-	-	-	-	-	-	-	-	56.835?	II.944	-
Plasma Conct.n	-	-	-	-	528	482	445	4I5	4I4	488	525	5I2
ved Plasma Conct.n	586	559	563	579	530	497	408	330	308	52I	540	53I
ombg.	-	-	-	5I.0	-	-	-	56.I	53.9	55.8	57.8	53.5
N.P.N.	-	-	-	-	-	-	-	63.I	68.I	44.4	22.6	-

Calculated Salt Content of the Subjects Body. I77.037 Grams.

lost 2659 cc. of fluid in excess of his intake and correspondingly his observed plasma sodium chloride concentration was slightly higher than his calculated. In order to emphasise the importance of dehydration in the production of increased concentrations of electrolytes in body fluids, on the second day of his depletion period his was

Experiment 3.

Guy Wickterman, aged 39.



given no intravenous fluids, and the fluid intake by mouth was limited to 240 cc. He thus lost an excess of 3780 cc. of fluid over his intake, making a total negative fluid balance of 6349 cc. His observed plasma sodium chloride concentration then became higher by I5 mgs.% than his calculated (497 mgs.% to 482).

On the third day of the depletion period the intravenous administration of 5% glucose solution was restarted and his intake of fluid by all channels was 734 cc. in excess of his output. At the same time, with the withdrawal of II.766 grs. of salt his observed plasma sodium chloride concentration fell to 408 mgs.% and, in part due to excess of the fluid intake over the output, his calculated plasma sodium chloride concentration was higher by 37 mgs.%.

On the fourth day of his depletion period a further 9.30I grs. of salt were removed and a fluid intake 794 cc. greater than his output was given. His observed plasma sodium chloride concentration should have been 4I5 mgs.%. This very marked discrepancy was due probably to the two factors which have been previously commented upon i.e., firstly dilution of electrolytes in the body fluids by the excess of the fluid intake over the output, and several unknown factors which affect the concentration of body electrolytes in extracellular fluids when low concentrations have been reached as the result of depletion.

On the fifth day of the depletion period it was decided to wait 24 hours before replacing any chlorides and merely to administer an excess of fluid by mouth in order to determine whether the plasma sodium chloride concentration would remain constant. He was given 34I4 cc. of distilled water by mouth and, if an insensible water loss of I200 cc. is assumed, his fluid intake of 34I4 cc. was I404 cc. in excess of his urinary output and insensible water loss. As the result of these measures the patient's observed sodium chloride concentration fell a further 22 mgs.% to 308 mgs.%. But, during this 24 hour period the sodium chloride content of his urine was 0.I05 grs. and, assuming his loss of sodium chloride through the skin was 0.3 grs. his calculated plasma sodium chloride concentration should have fallen only I mg.%. That is, as the result of dilution of his depleted body electrolytes by approximately 3.5% ($\frac{1404}{40,000}$ assuming his body fluids had been reduced to between

59 and 57% of his total body weight), the concentration of sodium chloride in his blood plasma fell a further 2I mgs.%. At this stage he passed into water intoxication.

Water Intoxication.

This condition is of considerable rarity, but should it occur in an aggravated form it may be fatal. Rowntree in an able paper (74) first drew the attention of the medical profession to this condition. He noticed that in patients suffering from diabetes insipidus who had been drinking from 8 to IO liters of water per day by mouth, if they continued to ingest these large volumes of water after the administration of pituitrin they developed headache, nausia, asthenia, in-coordination, and a staggering gait. In other words symptoms and signs of increased intracranial pressure. He then conducted a series of experiments on animals in which water in excessive amounts was administered by mouth. Such excessive water administration caused a decrease, up to 25%, in the sodium chloride concentration of the blood plasma, and the concentration of potassium exhibited the same dilution. The animals also showed asthenia, muscular irritability, convulsions and finally in many cases death followed. At autopsy cerebral oedema was a constant finding and Rowntree attributed the convulsive seizures and subsequent death of the animals to cerebral oedema, and showed that convulsions could be prevented by decompression of the skull. He also showed that it was impossible induce this condition of water intoxication in animals that had been given IO% sodium chloride solution immediately before the administration of water.

In I935 the first fatal human case which was recognised to be due to water intoxication was reported by Helwig, Schutz, and Curry (75) in a woman aged 50 who had a cholecystectomy performed for cholelithiasis. After operation she was given tap water per rectum and over a period of 30 hours post operatively she absorbed 9000 cc. and excreted 2350 cc. of fluid in urine and vomitus. Assuming that she lost in the 4I hours that she lived post operatively approximately 3000 cc. of water in insensible perspiration, her intake of fluid over her excretion was approximately 3650 cc.

The symptoms and signs observed during the period she lived post operatively were neck pain, vomiting, severe headache, tremor of the right arm, passing on to stupor, convulsions, dilation of the pupils and opisthotonos and death. During the whole period she perspired freely.

Fortunately this supremely interesting case came to autopsy which was performed within one hour after death, when neither rigor mortis nor livor mortis was present. The following is a summary of the post-mortem findings.

"The body was still quite warm. External inspection was not noteworthy. Edema was not present.... The liver was somewhat enlarged. It weighed 1800 grams and showed a slick, moist cut surface with quite indistinct lobulation.... Descending and sigmoid colons were almost spastic, while the remainder of the bowel was of about normal caliber. In the chest the lungs were freely crepitant and no excess of fluid was present in the pleural or pericardial cavities.

"The cranial cavity was then investigated. The scalp and skull presented nothing of pathological importance. When the skull cap was removed, the dura mater was found to be stretched tightly and the underlying brain was of striking apperance. The sub-arachnoid space seemed to be completely obliterated and the pia-arachnoid was almost bloodless. The cerebral convolutions were very much flattened and the sulci appeared in most instances to be completely obliterated, being seen as fine lines coursing over the cerebral hemispheres. No sub-arachnoid fluid was present and the brain surface presented a rather dry appearance. After the brain was removed it was found to be uniformly swollen in all diameters and gave the impression that it had been crowded into the cranial vault, having an appearance not dissimilar to internal hydrocephalus. When the ventricals were opened however, instead of being dilated they seemed to be actually reduced in diameter and a maximum of 2 cc. of clear fluid lay on the floor of each ventricle. The choroid plexus contained a cyst of about 2mm. in diameter in the left lateral ventricle and the whole plexus appeared swollen and edematous. Cross section through the brain showed a smooth homogeneous wet appearing surface and in the cerebral cortex the outlines between the white and the grey matter were much more indistinct than normal.Careful inspection of the vessels showed no note-worthy alteration. No haemorrhage or foci of encephalomalacia were seen. The brain weighed 1440 grams.

Microscopic Changes.

"The lungs, liver, brain, kidneys, and bowel were the only organs showing any alterations from the normal." For the purpose of this paper only the microscopic changes in the brain will be reported.

"The brain showed an apparent increase in the vacuolisation of the stroma, with what appeared to be an increase of the caliber of the peri-vascular and peri-neural spaces.... The brain tissue surrounding the external limiting membrane of the peri-vascular spaces was quite edematous and frequently showed a rather poorly defined, faintly reticulated false space immediately adjacent to the limiting membrane.... The choroid plexus was distinctly edematous. The ependymal cells were swollen and vacuolated and were undergoing proliferation and, in many areas, desquammation."

Helwig, Schutz, and Curry then conducted a series of experiments on rabbits in which animals weighing approximately 1000 grams were given 50 cc. of tap water by rectum every thirty minutes. After the administration of 300 to 400 cc. there was only a marked increase in the urinary output with reduction in its Specific Gravity. After 500 cc. The urinary output decreased and the animals began to salivate. They thereafter became restless and fine fibrillary twitchings of the ears and muscles of the extremities were noticed. Within the next hour after a further 100 cc. had been administered these fine fibrillary twitchings were replaced by clonic convulsions and opisthotonos, dilatation of the pupils, and a marked decrease in the urinary output. Death finally supervened during a convulsion.

The blood showed a consistent decrease in chloride ranging from 100 to 240 points. Blood increased in about half the animals and the CO_2 combining power was decreased. The gross and microscopic pathological changes of the animals were the same as those of the fatal human case.

Chemical Studies. All the tissues of the body except the liver showed a marked decrease in chlorine content; in the brain this change was especially marked and amounted to a 50% decrease from the normal.

Helwig, Schutz, and Kuhn have recently reported another case of water intoxication which was successfully treated by the intravenous administration of sodium chloride. This case was one of a woman aged 64 who was submitted to a pan hysterectomy and appendicectomy, and, after operation absorbed approximately 8250 cc. of water from the rectum. She developed similar symptoms to those described in the first case, coma, convulsions, opisthotonos, cyanosis, Cheyne-Stokes respiration, and a bilateral Babinski sign. At this time her plasma sodium chloride concentration was 380 mgs.%. About 12 hours later after the administration of 6 grams of sodium chloride her plasma sodium chloride concentration was 350 mgs.% and the CO2 combining power was 32 volumes per cent. As the result of this administration of salt her sumptoms and signs were slowly relieved and she recovered.

Discussion of the mechanism of water intoxication will be postponed until after the history of our experiment on G.W.

It will be remembered that on the fifth day of the depletion period it was decided not to restore the body chlorides to normal immediately but to wait and determine the effect of the administration of a large quantity of water rapidly. During the day he had drunk less than 500 cc. of water, had lain in bed and only suffered from muscular cramps when he moved. His pulse was about 80 per minute with the typical low pulse pressure which occurs in states of hypochloraemia. At 8 p.m. he was given 3 liters of water and urged to drink this at the rate of 500 cc. an hour, and by 11.30 p.m. all the water had been consumed. He was then completely rational and complained only of slight headache.

By early the following morning he became irrational, restless and completely unco-operative. If spoken to he appeared not to understand what was said although he seemed to listen. He continually held his head as though suffering from headache and was apparently photophobic because he repeatedly turned away from the light. He was abusive at the least interference and picked continually at his bed clothes; he was not salivating but repeatedly licked his lips; his skin was flushed and he was slightly cyanotic. his eyes seemed to protrude somewhat and his appearance suggested thyrotoxicosis. He repeatedly retched but did not vomit.

On examination his pupils were very small and did not react to light. There was apparently no myotatic irritability but this is difficult to state definitely because of his restlessmess. There was a bilateral flexor plantor response. The knee jerks etc. were difficult to elicit. His neck was stiff and flexion of the neck was resented. His pulse showed considerable alteration in character from the day before. It was now rather slow and full. The blood pressure was not determined but it appeared slightly above normal to the finger.

The necessary manoeuvres for withdrawing blood and starting an intravenous drip apparatus were fiercely resented, and he had to be tied down. The blood withdrawn was very dark in colour. After about I200 cc. of 0.85% sodium chloride solution had been run in his condition was somewhat quieter. He was then given about I000 cc. of glucose and this produced some relapse and he became so restless that in spite of being tied down he managed to cause the needle to perforate the vein and the intravenous infusion was temporarily discontinued.

By II.30 it was realised that his bladder was probably enlarged as there was nearly four fingers of dullness to percussion above the symphysis pubis and he was therefore catheterised and 850 cc. of clear urine were removed. This manoeuvre seemed to quieten him considerably and he thereafter slept for about two hours. At this time his blood non protein nitrogen was 68.I mgs.%.

At I.30 p.m. a further intravenous infusion was started. I550 cc. of saline was administered rapidly and about 850 cc. of 5% glucose solution. He thereafter became more restless and wild and managed to break the air trap of the intravenous drip apparatus. He was catheterised again with great difficulty at 5.30 p.m. and 2I0 cc. of urien were withdrawn.

At 7 p.m. he was given 5 grains of sodium luminal subcutaneously. he remained so restless and abusive that at I0 p.m. he was given 9 drams of paraldehyde per rectum and thereafter he slept for about 30 minutes. Up to this time there was no significant change in his clinical condition except that his pupils during the day had gradually enlarged but were still not reactive to light.

Clinical studies having been continued long enough and the condition being one of considerable danger, it was decided to restore the osmotic pressure of his extra-cellular fluids and dehydrate the brain by the administration of hypertonic sodium chloride solution. His plasma sodium chloride concentration being 308 mgs.%, the calculated weight of sodium chloride needed to restore the normal sodium chloride content of the body to normal was 76.677 grams. Two liters of a solution of twice normal sodium chloride was made up and it contained 34.0 grams of salt. This was administered through a Levine tube passed through the nose into the stomach and 200 cc. were administered every thirty minutes.

Improvement rapidly followed and by 7 a.m. he was virtually normal again, being completely orientated and co-operative. The pupils became equal, of normal size, and reacted to light and accomodation. His skin was moist and a little flushed; he had no headache. His nervous system gave no evidence any abnormality; he had absolutely no memory of the happenings of the previous 24 hours, his last recollection being that of going to sleep. His pulse was of normal rate and volume. He was considerably surprised to find several bruises on his body which he had incurred in his struggles of the day before.

Unfortunately for the accuracy of the chloride replacement studies, during the previous night he passed three large fluid stools which the nurse threw away. The passage of these stools was presumably due to the administration of hypertonic saline by mouth, and each was said to measure about I000 cc. Assuming that the concentration of sodium chloride in these stools was 5grams per liter, the sodium chloride lost through this channel was about I5 grams. It was however decided to neglect these losses and to administer the difference between the calculated socium chloride requirement of 76.677 grams and that administered the previous day, 57.37 grams. An intravenous infusion was therefore given containing 22.755 grams.

As a result of the previous day's salt administration his plasma sodium chloride concentration had been raised to 52I mgs.% from the previous level of 308 mgs.%. A further 22.755 grams of sodium chloride was administered of which II.944 grams was retained. Neglecting the losses of salt which must have occurred in the liquid faeces which the subject passed while in water intoxication, the total salt retention of the replacement period was 67.629 grams which, by calculation, should have raised the plasma sodium chloride concentration to 525 mgs.%. The actual level reached was 540 mgs.%. It will be noticed that, in contradistinction to the first two cases, this observed plasma sodium chloride concentration is in excess of the calculated. During this phase of the replacement period it was therefore expected that during the final day of study there would be a fall in the plasma sodium chloride concentration and excretion of sodium chloride in the urine. Both occurred, the plasma sodium chloride concentration falling to 531 mgs.% and 4.167 grams of salt were excreted in the urine. The reasons for this have been already discussed but it bears repetition here that:

1. The kidney has no true critical plasma sodium chloride concentration below which the excretion of chloride in the urine ceases.(Ambard stated that there was such a critical at a concentration of about 560 mgs.%.)
2. That only the amount of salt which can be dissolved in the body fluids of the subject at the time of administration to form a solution of normal osmotic pressure and chemical composition will be retained.
3. That for the satisfactory administration of sodium chloride it must be given in a solution of not more than normal physiological strength. It is probable that the ideal strength of solution for the administration of sodium chloride is between a concentration of 0.7 to 0.8%

During the period of chloride depletion there was an increase in the blood non protein nitrogen which reached a maximum of 68.1 mgs.% but,after the body sodium chloride had been restored nearly to normal,there was a fall in this concentration of non protein nitrogen nearly to normal. This phenomenon will be discussed in the next experiment on H.A.

The clinical phenomena of the period of water intoxication have been discussed in some detail. All the other features of salt depletion were also noted in this case, but it is noteworthy that the muscular cramps were not so severe on the fourth day of his depletion period when his plasma sodium chloride concentration was 330 mgs.% as they were on the third day when his observed plasma sodium chloride concentration was 408 mgs.%. There is at the moment no adequate explanation for this feature of the case. Again, after the replacement of sodium chloride, he experienced the same feeling of extra well being already noticed by R.W.and S.T., and was discharged on the twelth day of the experiment looking and feeling well.

Discussion on Water Intoxication.

It is not yet possible to discuss with absolute assurance the details of the pathology of water intoxication and further work will be carried out on this subject. However, the following is a tentative explanation of the condition.

It will be remembered that in the discussion on the experiments of Darrow and Yannet (27), it was stated that, if the osmotic pressure of the extracellular fluids be lowered, as the glucose experiment, by the withdrawal of extracellular electrolytes, in order to equalise the osmotic pressures of the intracellular and extracellular fluids, water must flow into the cells. In our case of water intoxication, the electrolyte content and consequently the osmotic pressure of the extracellular fluids had been lowered by the depletion of the sodium chloride content of the body. This caused a transference of water into the cells in order to reduce the osmotic pressure of the intracellular fluids correspondingly. At this point a large dose of water was given and, passing into the extracellular fluids it further lowered their osmotic pressure. As the result there was a further transference of water into the cells to reduce the osmotic pressure of the intracellular fluids to a level equal to that of the extracellular fluids. In other words, a cellular water plethora was produced. The only tissues which are unable to swell considerably are those of the brain as they are confined inside the inelastic skull. Each individual brain cell swelled and therefore it was necessary for the brain as a whole to occupy more space. At first the increased demand for space was met by the extrusion of the cerebrospinal fluid from the cranium, but a point was reached at which no further cerebrospinal fluid could be extruded. The brain then became increasingly compressed and cerebral anaemia supervened. As a result of these changes, the symptoms and signs of cerebral compression were produced and, if compression of the brain had been sufficiently severe and prolonged death would have occurred.

In order therefore to counteract this cellular water plethora of the brain it is necessary to increase the osmotic pressure of the extracellular fluids and withdraw water from the cells. This is most rapidly effected by the intravenous administration of 50% sucrose solution as the sucrose molecule is incapable of traversing the cell membrane and exerts a considerable osmotic pressure. In our case this procedure was considered but was not adopted as the subject was not judged to be extremis. He was therefore given sodium chloride in hypertonis solution which also causes an increase in the osmotic pressure of the extracellular fluids but less rapidly and less marked than does sucrose. As the result of the increase in the osmotic pressure of the extracellular fluids water was transferred from the cells to the extracellular fluids and the volume of each brain cell thereby reduced, and also of the whole brain. The excessive intracranial pressure was thereby relieved, with a return of the subject to normal.

The discussion of water intoxication has been of necessity brief, and to a large extent theoretical. However the possibility of such a condition occurring after the administration of fluids either by mouth, by rectum or intravenously, emphasises the importance of disturbances in the water salt balance of the body. Minor degrees of cellular water plethora can occur even in normal individuals, as has been recorded by Amberg and Austin (Cited by Rowntree,74). These authors noted that during experiments on skin elasticity in which they drank 3000 cc. of water in a period of 20 minutes that such severe muscular twitchings occurred that they were unable to make elastometric measurements. In abnormal persons whose body electrolytes have been depleted by disease, cellular water plethora may even be fatal. Any reduction of the normal electrolyte content of the body is harmful; reduction in the sodium chloride content of the body to about 50% of the normal is potentially so dangerous that many observers have considered that this degree of depletion constitutes the lowest limit compatible with life. Therefore, to minimise morbidity and avert mortality, it is incumbent on the surgeon to ensure that, as far as possible, his patient shall be in the best possible condition for operation and that post operatively they shall be maintained in electrolyte balance.

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Experiment 4.H.A. Page I09 Correction.

With reference to the concentration of serum proteins read Grams per cent for milligrams per cent.

Experiment 4.

The fourth subject, H.A., was a healthy normal young man aged 24 who was by trade a cowboy. Psychologically he was not entirely satisfactory as he disliked being confined indoors for as long as twelve days. He also did not drain very rapidly. Table I8 summarises the data obtained and Figure 6 depicts graphically the daily weight, observed and calculated sodium chloride concentrations, the daily difference between the intake and output of water, and the concentration of the plasma proteins. The objects of this experiment were:

I. To determine definitely the effect on the observed plasma sodium chloride concentration of dehydration and overhydration of the subject.

2. The effect on the blood non protein nitrogen of chloride depletion while maintaining an adequate excretion of urine.

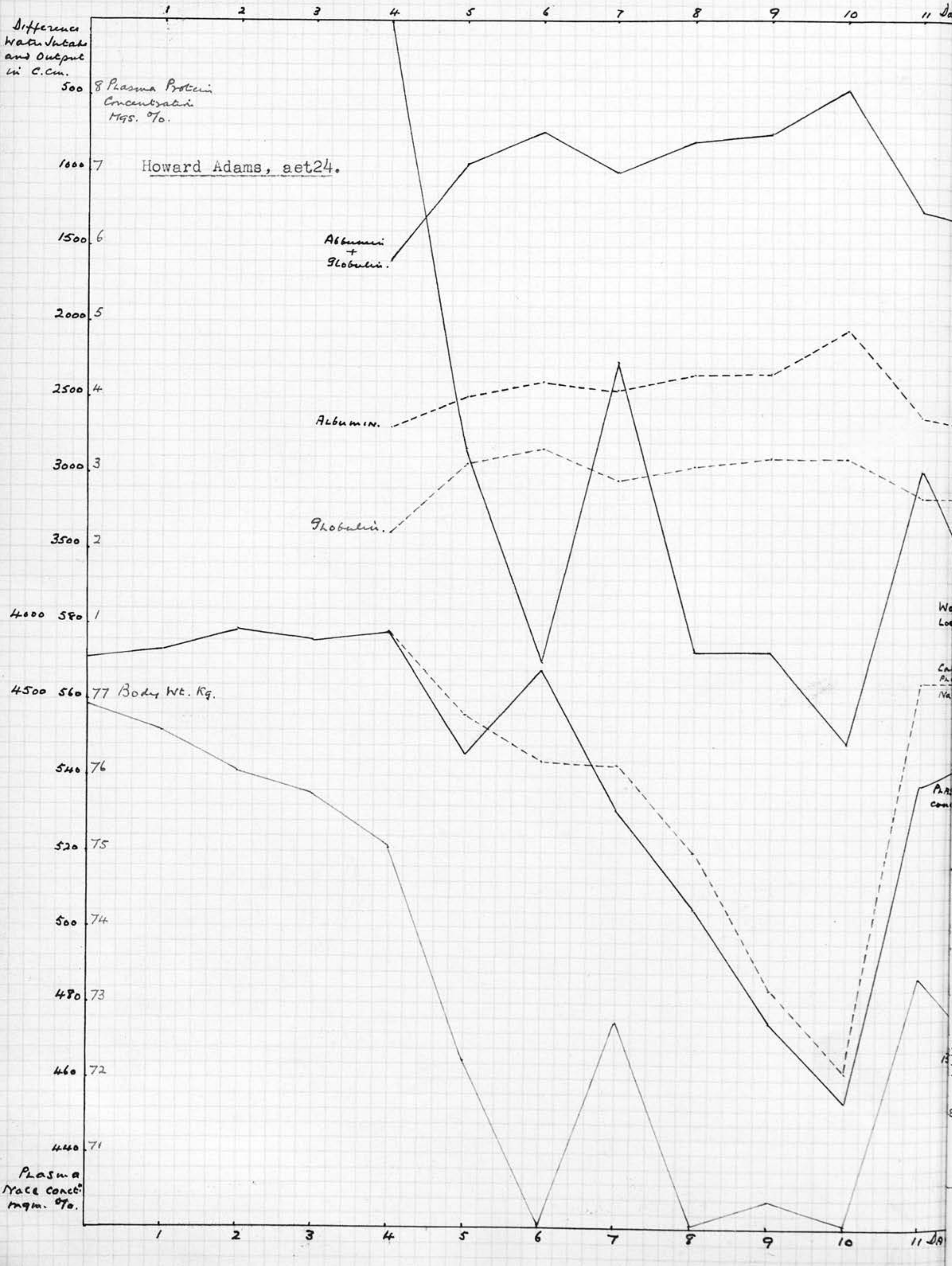
3. To determine the effect on the concentration of the plasma proteins of depletion of extracellular electrolyte with consequent reduction in the volume of the extracellular fluids.

It will be seen that:

I. Throughout the whole period of study the observed and calculated plasma sodium chloride concentrations agree closely. On the first day of the depletion period there was a difference of I0 mgs.%, the calculated being higher than the observed plasma sodium chloride concentration.

On the second day he was again given only a small volume of water by mouth, 520 cc., and in spite of the further loos of 3.964 grams of salt he observed plasma sodium chloride concentration rose from 546 to 568 mgs.% when his calculated concentration had fallen to 544 mgs.%. His negative fluid balance at this point was 4252 cc. In other words, as the result of dehydration, the electrolyte concentration in the body fluids rises.

On the third day of the depletion period the gastro intestinal drainage was discontinued and he was given 674I cc. of distilled water by mouth to drink. During the day he lost only a total of 0.346 grams of sodium chloride. As the result of hydration his observed plasma sodium chloride concentration fell from 568 mgs.%


Howard Adams, aet24.
Difference Water Intake and Output in C.cm.
8 Plasma Protein Concentration Mgs. %.
Albumin + Globulin.
Albumin.
Globulin.
77 Body Wt. Kg.
Plasma NaCl Conct. mgm. %.
1 2 3 4 5 6 7 8 9 10 11 Days
500 1000 1500 2000 2500 3000 3500 4000 4500
580 560 540 520 500 480 460 440
8 7 6 5 4 3 2 1
77 76 75 74 73 72 71

H.A.

TABLE 18.

Jan.	19	20	21	22	23	24	25	26	27	28	29	30
t.	76.59	76.04	75.74	75.03	72.27	70.01	72.73	70.05	70.39	70.05	73.36	72.39
Cals.	-	1553	2272	1500	400	400	400	2714	935	912	1320	1570
NaCl	-	0.661	0.&56	0.229	-	-	-	0.297	-	-	0.208	0.320
(Mouth	-	-	-	-	360	520	6741	420	1480	985	1410	1720
s((I.V.	-	-	-	-	-	-	-	4192g	3671g	3061g	4426s	-
(	-	-	-	-	2010	900	-	2310	1640	1510	-	-
age((NaCl	-	-	-	-	6.613	3.015	-	10.511	7.938	6.448	-	-
(Vol.	2475	1630	1810	1320	-	822	3560	3005	2310	1740	3045	1400
((NaCl.	10.765	3.048	2.100	0.766	-	0.649	0.046	0.270	Nil.	0.122	0.609	0.098
Skin	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
NaCl	Preliminary Period.				Depletion Period Losses.						Replacement.	
	11.065	15.074	18.230	19.255	6.913	10.877	11.223	22.007	30.245	37.115	0.909	0.398
rence In:Out.	-	-	-	-	2850	1402 4252	1981 2271	1903 4174	1 4173	404 4577	1591 2986	880 3866
Given.	-	-	-	-	-	-	-	0.297	-	-	37.829	0.320
etained	-	-	-	-	-	-	-	-	-	-	36.920	-
Plasma Conct.^{n}	-	-	-	-	556	544	543	520	484	462	565	565
ved Plasma Conct.^{N}	573	578	576	578	546	568	531	505	475	454	538	545
omb.^{g} .	53.8	-	-	55.8	51.7	53.1	56.3	49.2	49.5	-	57.9	60.7
N.P.N.	-	-	-	30.5	32.5	42.3	30.1	33.3	37.5	40.2	35.5	32.1
Proteins.												
in.	-	-	-	3.6	4.0	4.2	4.1	4.3	4.3	4.9	3.8	3.6
lin.	-	-	-	2.2	3.1	3.3	2.9	3.1	3.2	3.2	2.7	2.7
Proteins.	-	-	-	5.8	7.1	7.5	7.0	7.4	7.5	8.1	6.5	6.3
atio.	-	-	-	1.6	1.3	1.3	1.4	1.4	1.3	1.5	1.4	1.3

Calculated Salt Content of the Subjects Body. 185.7 Grams.

to 53I mgs.% during a period in which he lost practically no salt, thus demonstrating that the concentration of body electrolytes may be caused to fall as the reult of over-hydration of the body.

During the remaining three days of the depletion period attempts were made to maintain him in fluid balance, and to observe the degree of correspondance between the calculated and observed plasma sodium chlòride concentrations. It will be seen that they agree very closely the lowest level reached being 454 mgs.%.

The replacement of the sodium chloride lost was carried out in one day, a total of 36.92 grams being given intravenously in 4426 cc. of water. His observed plasma sodium chloride concentration finally reached 545 mgs.% and it was intended to continue the experiment for a further day to obtain the expected rise in the observed plasma sodium chloride concentration which would have occurred but the "call of the wild" became too srong for our cowboy and he left hospital for the "great outdoors".

2. The Blood Non Protein Nitrogen Concentration.

The concentration of the blood N.P.N. became greater during the first two days of the depletion period as the result of dehydration and the excretion of only 2I42 cc. of urine during the two day period. On the first day he actually excreted no urine. This effect was therefore very largely due to the excretion of an inadequate volume of urien.

On the third day in which he drank 674I cc. of distilled water he excreted 3060 cc. of urine, and, partly as the result of washing out the accumulated urinary waste products and partly from dilution of the body fluids the concentration of non protein nitrogen in the blood fell to 30.I mgs.% from 42.3 mgs.%. During the succeeding three days he excreted 3005, 23I0, and I740 cc. of urine and yet his blood non protein nitrogen concentration gradually rose again, eventually to 40.2 mgs.%. This effect I believe to be due to an effort on the part of the body to maintain the total osmotic pressure of the body fluids by the retention of urea etc. The products so retained having no effect on the partition of water between cells and extracellular fluids and only raising the total osmotic pressure of the body fluids as a whole.After the administration of salt which raises the electrolyte osmotic pressure of the body fluids the body allowed the no longer necessary urinary waste products to be excreted.

3. The Plasma Protein Concentration.

The concentration of the plasma proteins followed the same general trend as did the concentration of non protein nitrogen in the blood. Unfortunately many factors influence the concentration of the plasma proteins, but it is interesting to observe in this case that, during the last three days of the depletion period there was a gradual rise in their concentration and in the replacement period there was a definite fall. If their concentration can be taken as an indication of the volume of the extracellular fluids, and especially changes in their concentration of alteration in the volume of extracellular fluids of which blood is one component, then their estimation becomes a valuable clinical procedure. I believe that a rise in the concentration of the plasma proteins indicates a decrease in the volume of extracellular fluids, and a fall in their concentration an increase in the extracellular fluid volume. The results of this experiment seem to substantiate the conception that the total volume of the extracellular fluids is dependent not only on the fluid intake but also as much on the amount of electrolytes present in the body to maintain a normal osmotic pressure of the body fluids as a whole; and that, unless the body have a normal electrolyte content, the administration of water alone will not effect an increase in the volume of the body fluids but will be excreted until the concentration of the available electrolytes present in the body is approximately normal. Therefore, to ensure that the fluid content of the patient shall be normal the amount of electrolyte in his body also must be normal. Further work is being carried out on this important practical problem.

The clinical effects of salt deprivation already recorded in the other three experiments were also observed in this case and it is unnecessary to repeat them here cramps were however mild in this case probaly because his observed plasma sodium chloride concentration did not fall below 454 mgs.%. He was discharged looking and feeling well.

SUMMARY.

1. Water and Salt metabolism has been discussed both in their theoretical and in their practical aspects.

2. A series of experiments was conducted on normal human subjects to prove or disprove certain conceptions of salt metabolism.

3. In general these conceptions were substantiated and, arising from this work the clinical applications are as follows:

A. To diminish the mortality and morbidity from operations both water and electrolytes must be given in adequate amounts to restore or maintain normality. Two main types of problem therefore, may confront the surgeon.

1. The case which comes under his care with depleted fluids and electrolytes and rules have been given for the restoration of both to normal.

2. The case which in hospital after operation loses electrolytes and fluids from vomiting, fistulae, etc. Such a case can be maintained in fluid balance by the application of the rules of water balance ennunciated by W.G.Maddock and detailed in this paper. The electrolyte balance can also be maintained by the administration of a volume of 0.9% sodium chloride solution equal to the volume of the abnormal fluid losses (vomitus, drainage from fistulae etc.) without endangering the patient by overloading him with sodium chloride.

B. The following table shows the degree of accuracy which results from the application of these rules, and I feel that, although much further work is needed fully to substantiate our claims, the clinical administration of sodium chloride has been placed on a sound basis.

TABLE 19.

Patient.	Body Weight Kg.	Initial Plasma NaCl Conct^n mg.%	NaCl Given Gm.	NaCl Retained Gm.	Calculated Optimal Retention Gm.	Plasma NaCl Concentration after Replac^t
J.W.	59.8	447	26.2	25.1	29.7	546
T.J.	72.7	427	40.6	40.6	42.7	564
W.P.	67.7	436	33.7	32.2	37.1	543
C.M.	63.6	404	55.8	40.9	43.8	559
D.C.	60.4	513	15.9	14.6	12.6	564
L.D.	60.2	372	70.1	49.4	50.1	566

In these cases the plasma sodium chloride concentration which we attempted to achieve after replacement was 560 mgs.%.

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